HEART.

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VENTRICULAR FIBRILLATION IN THE RAT'S HEART.

By J. A. GUNN.

(From the Pharmacology Laboratory, Oxford.)

ONE of the facts which has been most clearly established in regard to fibrillation of the heart is the extraordinary difference in the susceptibility of the hearts of different species of animals to this condition. Thus in regard to the isolated heart, "spontaneous" fibrillation occurs not infrequently in the cat's heart : rarely, if ever, in the rabbit's heart. A similar difference holds good in regard to the facility with which fibrillation is artificially produced in the hearts of those animals : e.g. by faradic stimulation of the heart's surface. Until recently[1] the rat's heart has not, to my knowledge, been used for perfusion experiments, and it has been found that the heart of this animal is even more liable to spontaneous fibrillation than is that of the cat. The frequent occurrence of fibrillation in the rat's heart has afforded many opportunities, not always welcome, of observing this phenomenon. I may, however, state at once that I have been no more fortunate than other observers in determining invariable antecedents of its spontaneous occurrence. In the experiments to be recorded the heart was perfused by Langendorf's method with Brodie's apparatus or some modification of it. As the perfusing solution Locke's formula (without glucose) was employed. The contractions were recorded by a hook in the ventricle connected with a lever in the usual way.

In the rat's heart there appear to be two (symptomatically but not necessarily fundamentally) distinct types of "spontaneous" ventricular fibrillation.

1. The first kind of fibrillation occurs in hearts which are beating regularly and well and with the usual frequency. Fibrillation of the ventricle comes on suddenly and may last for a few seconds and as suddenly disappear, giving way to the resumption of contractions slightly, if at all, deteriorated in rate and amplitude from those which obtained before the onset of fibrillation. A single attack of such fibrillation rarely leads to permanent arrest of the ventricle. Usually fibrillation recurs several times, often with complete temporary or (during the time of the experiment) permanent recovery. In those cases in which recovery from fibrillation does not take place, fibrillation passes off into permanent arrest of the ventricle in the systolic condition.

The characteristics of this type of fibrillation are, therefore, (1) its sudden occurrence in a heart which is beating well : (2) the possibility of its recovery ; (3) its giving rise, when recovery does not take place, to systolic arrest of the ventricle.

Those effects, following closely on one another, are shown in Fig. 1, where a first attack of fibrillation occurring suddenly is followed by almost complete reinstatement of the ventricular contractions, a second attack by deterioration of the contractions, and a final attack leads to permanent systolic contraction of the ventricle.

It has long been known that ventricular fibrillation may be induced by occlusion of the coronary arteries. In the perfused heart a simple method of producing fibrillation for demonstration—or for some experimental—purposes is by blocking the coronary arteries by admitting an air embolus into the fluid in the perfusion cannula. When ventricular fibrillation is
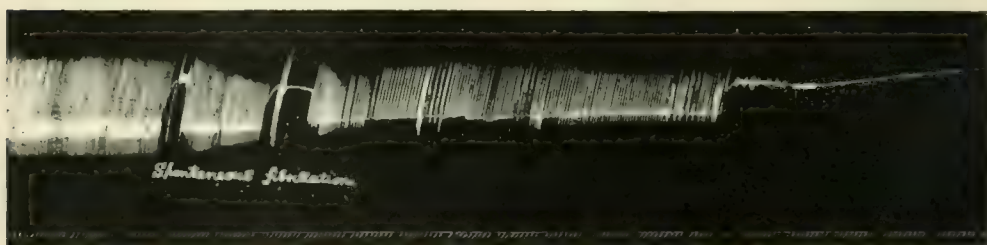
Fig. 1.—Showing spontaneous fibrillation of rat's ventricle, leading to systolic arrest.
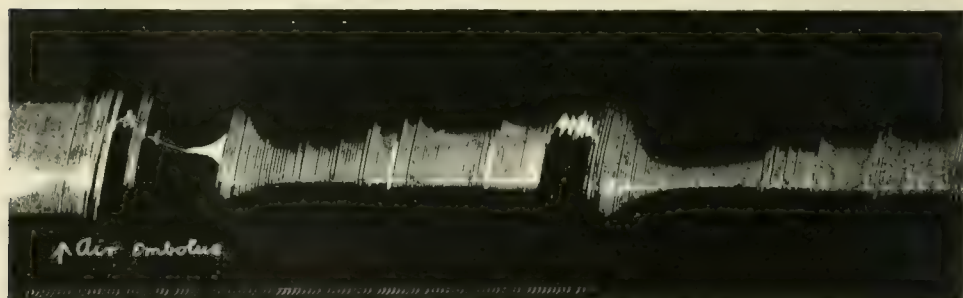
Fig. 2.—Showing fibrillation of ventricle produced by air embolus in the coronary vessels.

produced in this way, the resultant effect is precisely the same as that described as the first type of fibrillation : that is to say (1) fibrillation may last only for a few seconds and recovery be complete : (2) it may recur (usually at a short interval after the first fibrillation) : or (3) it may pass into permanent arrest of the ventricle in the systolic position.

Fig. 2 shows ventricular fibrillation produced by air embolus. A second fibrillation occurred about a minute after the first (possibly due to the further passage of air through the vessels) and the heart showed no further signs of fibrillation during the remaining time of the experiment (30 minutes).

2. The second type of fibrillation is met with under the following conditions. A heart may beat infrequently from the beginning of perfusion,

or it may begin at the usual rate and the frequency diminish gradually or
suddenly, the heart in either case eventually beating slowly, but not feebly,
and with long diastolic pauses. The ventricle may then begin to fibrillate
in a very definite way. Every, or almost every, contraction of the ventricle
is followed by a longer or shorter period of fibrillation, after which the ventricle
relaxes into the position usual to it at the end of diastole. A diastolic pause
ensues followed by a normal contraction which again gives rise to fibrillation.
This condition may persist for many minutes, fibrillation being in some way
consequent (in time) upon the ventricular contraction. This kind of
fibrillation leads to arrest of the ventricle in diastole, and I have on no
occasion seen the resumption of normal regular contractions following this
type of fibrillation.

Varieties of this type are illustrated in Fig. 3 and 4 which are tracings
taken from the same heart. Fig. 3 shows short periods of fibrillation
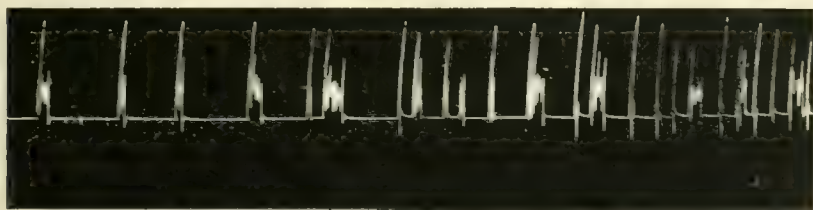
Fig. 3.
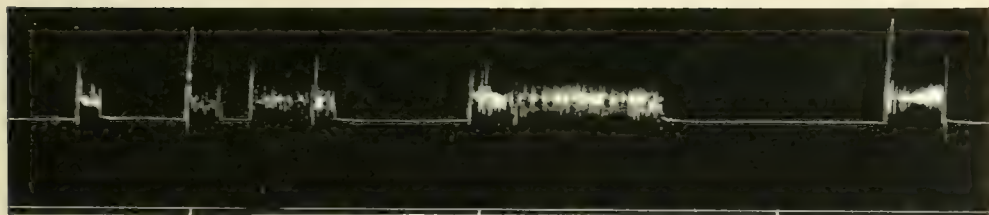
Fig. 4.

occurring after the majority of co-ordinate contractions ; Fig. 4 shows, with
longer diastolic pauses, the occurrence of more prolonged fibrillation after
every co-ordinate contraction.

The characteristics of the second type of ventricular fibrillation are,
therefore, (1) its occurrence in hearts which are beating infrequently ; (2)
non-recovery ; (3) resultant arrest of the heart in the diastolic position.

I have not been able to find in former reports any such differentiation
of ventricular fibrillation as that described above. However, upon considera-
tion of the researches of MacWilliam[2] on fibrillar contraction of the heart,
I have formed the opinion that he met with the same two varieties of
ventricular fibrillation, though this cannot be stated definitely as he submits

no tracings. He describes one class of cases of fibrillation as " a phenomenon of irritation induced by the action of various recognised stimulants." This kind of fibrillation is produced, for example, by faradic stimulation of the ventricle, and its occurrence is favoured, and its duration prolonged, by causes that augment the cardiac irritability. Recovery of the co-ordinate contractions occurs readily when fibrillation is produced in this way. This, I believe, approximates very nearly to the conditions under which I have found the first type of fibrillation. MacWilliam describes a second class of cases in which " the fibrillar contraction is induced by the more or less sudden action of certain influences of a depressing nature," such as the intravenous injection of a strong solution of potassium bromide. He states that, when ventricular fibrillation is produced in this way, " single contractions may occur after the rapid quivering movement has ceased, but they appear to be fibrillar in their nature, and any contractions excited by single induction shocks in such circumstances appear to be of the same character." He observed no recovery from fibrillation produced in this way. This description suggests strongly the second type of fibrillation which I have described as occurring in a slowly beating heart and, therefore, presumably in a condition of depressed vitality. It appears highly probable that, if a tracing had been shown by MacWilliam of the effect of an induction shock on the ventricle under the influence of potassium bromide, it would have revealed a normal contraction lapsing immediately into fibrillar contractions (as in Fig. 3), or, in his own words, single contractions fibrillar in nature.

The increasing recognition of the clinical importance of auricular fibrillation suggests the propriety of accumulating further data in regard to the experimental occurrence also of ventricular fibrillation, for the latter condition may yet find a place among clinical irregularities of the heart, though possibly only as a terminal phenomenon. As far as can be said from the observations recorded here, it is conceivable that either type of ventricular fibrillation described above might occur in an intact animal without causing so complete a failure of the circulation as to be immediately fatal to life.

A point of some interest is the stage of the cardiac cycle at which (spontaneous) fibrillation occurs. It can be seen in Fig. 1 and 2 that, in the beating heart, fibrillation never comes on during the systole of the ventricle nor during the early part of the diastole, that is to say it occurs only after the refractory period of the ventricle has passed off. It would seem justifiable to draw the deduction that the fibrillar contractions are subject to the usual law of the co-ordinate contraction, namely, that they can occur only when the heart has recovered from its refractory period.

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[2]   MacWilliam.   Journ. of Physiol., 1887, viii, 296.

A CASE OF TRANSIENT COMPLETE AURICULO-VENTRICULAR DISSOCIATION, SHOWING CONSTANTLY VARYING VENTRICULAR COMPLEXES.*

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A NUMBER of cases showing complete auriculo-ventricular dissociation have been reported, in which no lesion in the auriculo-ventricular bundle was seen or, at least, no lesion sufficiently large to destroy its substance and to block impulses passing from auricles to ventricles. In the curves made from these patients, both auricular and ventricular contractions were regular, and the outlines of the electrocardiographic curves, when these have been published, representing these contractions, especially the ventricular ones, were all uniform. The description of the case which follows is reported because it represents a variation, which has not yet been observed, from instances in this group. The dissociation which was present disappeared, so that no permanently damaging lesion of the bundle could have been present, and in so far this case belongs to the group described. It differs from the others in that the ventricular complexes were not uniform, but changed from beat to beat.

The patient entered the hospital† for the first time on August the 19th, 1910. He had measles and small-pox in childhood, but denied ever having had syphilis, gonorrhœa or any other infection. His habits were good; he drank whisky occasionally, but did not smoke. For fifteen years he coughed during the winter months and had profuse expectoration. For the few years previous to admission he complained of shortness of breath on exertion, but two years before, the dyspnœa increased so that he was no longer able to sit bent over his work. At the same time he began to suffer from occasional palpitation and to complain of œdema of the legs. At first these symptoms kept him from work, but did not oblige him to go to bed. A month before the cough and dyspnœa became so severe that he was obliged to sit up in bed at night. He had no anginal attacks or fainting spells. His appetite was very poor, his bowels were constipated. Urination was frequent and occurred several times each night.

On physical examination, his general condition and nourishment were good. He had general œdema of the subcutaneous tissues and a slight yellow tinge of the skin and conjunctivæ. He had dyspnœa and orthopnœa. His pupils were normal. His lips were cyanotic. His teeth were in poor condition; he had pyorrhœa of the gums. There were signs of stasis at the bases of the lungs behind, but these showed no other abnormal physical sign. The apex of the heart was neither visible nor palpable. The right border of cardiac dulness was at the right border of the sternum. The left border was 14·5 cm. from the median line in the sixth space. The sounds were heard best in the fifth space 13 cm. from the mid-sternal line. They were rather faint. The quality of the first sound was valvular and was accompanied by a blowing systolic murmur, transmitted to the axilla. At the base both sounds were accentuated, that at the aortic area being the louder. The radial pulses were equal, normal in rate, of good force and quality. The rhythm was very irregular. The liver was enlarged and was felt three fingers'

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* A short account of this patient was published in the Proc. Soc. Exp. Biol. and Med., 1911, ix, 24.

† He was treated on the First Medical Division, Mount Sinai Hospital, New York. I am indebted to Dr. J. Rudisch and to Dr. N. E. Brill for permission to report the history.

breadth below the border of the last rib. It was extremely tender. The spleen was not felt. The abdomen showed no abnormality. The legs were œdematous, cyanotic and cold. A knee jerk was not obtained. The systolic blood pressure was 150 mm. Hg. The amount of urine varied between 800 to 1,200 cc. per day ; the specific gravity was 1,010 to 1,022 ; it contained a faint trace of albumin. Polygraph tracings (Fig. 1) showed coupled rhythm. In the first three days of his stay in the hospital he was given eight ounces of the infusion of digitalis. On the day of admission the pulse rate was 80, and on the third day, the day digitalis was stopped, 56 was the lowest rate recorded. The rhythm was irregular and not every heart-beat caused a palpable pulsation in the radial artery. On the day of discharge, the action of the heart was regular.

The patient was admitted to the hospital a second time on November the 20th, 1910, two and a half months after discharge. He had been well for two weeks, but then his symptoms, œdema of the legs and increasing dyspnœa, recurred. On admission his general condition and physical examination were much like those on the first admission. He was discharged on December the 1st, 1910, much improved.

Twenty-five days later (December the 25th, 1910) he was admitted for a third time. He felt well for two weeks after discharge, but the old symptoms, œdema of the legs, dyspnœa and orthopnœa reappeared. He complained now also of palpitation and oliguria. Examination showed the same general physical condition that had been present before.

He was admitted a fourth time one month later (February the 10th, 1911). He had been well the first two weeks at home, but the second two the same symptoms reappeared. His general condition was good. He had orthopnœa and slight dyspnœa. There was cyanosis of the lips. The skin and conjunctivæ had a subicteric hue. He had the signs of pulmonary emphysema and stasis at the bases of both lungs behind. The left border of the heart extended to the nipple line. The sounds and the murmur were as they had been before. The rate was 45 per minute and regular. The liver was felt a finger's breadth below the margin of the ribs. The edge was even and the liver tender. Polygraph tracings (Fig. 2), made at this time, showed that incomplete block (2 : 1) of the auricular impulses was present. On the 11th and 13th electrocardiograms showed the presence of complete dissociation (Fig. 3 to 5). A polygraph curve (Fig. 6), made on the 17th, also showed complete dissociation. On February the 15th he had signs of increasing heart failure. He began to take eight minims of the fluid extract of digitalis a day. On the 18th the rate of the radial pulse was 40 to 42. On the 20th the amount of the drug was reduced to four minims a day and was continued until February the 22nd. He took forty-eight minims in all. On February the 23rd the systolic blood pressure was 190. On the 25th his condition was improved ; he had none of the subjective symptoms of heart failure. The pulse rate was 40 and regular. He was given atropine gr. 1 75 hypodermically, but the injection had practically little effect on the heart. Both auricular and ventricular rates were slightly elevated ; auricles and ventricles were 70·50 and 44·82 before and 76·2 and 48 after the injection respectively. On the 27th the systolic blood pressure was 165. The rate of the auricles was 61·8 and of the ventricles 40·8. Atropine gr. 1 50 was given hypodermically. The auricular rate rose to 74·4, but the highest ventricular rate was 45·2. After this his radial pulse rate rose to 68. On March the 1st the systolic blood pressure was 172 and the diastolic 60. On the 3rd it was 170. He had no œdema. March the 4th the pulse rate was about 60. Polygraph curves and electrocardiograms showed a normal 1 : 1 rhythm. He was discharged on March the 7th, having a pulse rate of 60.

The patient was examined again on December the 19th, 1911. The last examination was made on February the 18th, 1913. On both occasions the rate and rhythm of his heart were normal (Fig. 7). He is now seventy years old, looks well and is well nourished. His condition has been good for the past two years. He has not been obliged to go to bed, although he has been somewhat weak and feeble and has suffered from moderate præcordial oppression and dyspnœa on climbing stairs. On examination his pupils react normally. There is hyper-resonance over the chest. The breath sounds are good, but there are numerous rales at the bases behind. The apex impulse is seen clearly in the fifth space 13 cm. from the median line. The impulse is felt but is weak. The right border of the cardiac dulness is 3·5 cm. from the median line in the third space and 4·3 cm. in the fourth. The left border is 9·3 cm. from the median line in the third, 12·5 in the fourth and 13·6 in the fifth spaces. The first sound at the apex is weak. The second sound is accentuated and followed by a high-pitched, blowing systolic murmur, transmitted to the axilla. At the base the second sound is faint, but at the pulmonic area it is relatively accentuated.

Description of the curves.

A number of polygraph curves were made on August the 22nd, 1910 (Fig. 1). In the radial curve there are successions of pairs of beats, the second followed by a pause almost equal to two of the shorter ones. The two radial beats are represented in the jugular curve by *c* waves and each

is preceded by an *a* wave. That portion of the venous curve which corresponds to the pause in the radial curve, contains an *a* wave midway between the second member of the first and the first member of the second group. The *a-c* interval of the first member of the group is 0·2 seconds, of the second 0·26 seconds, while the third *a* wave is blocked. The patient had taken digitalis for three days at this time, so that it is likely that the arrhythmia was the result, as it so often is, of digitalis poisoning.
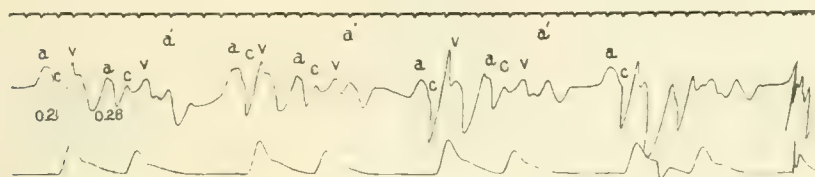
Fig. 1. Polygraphic curve of the movements of the jugular vein and radial artery, August the 22nd, 1910. The upper line shows the time in 0·2 seconds. A coupled rhythm is seen in the radial curve. In the jugular curve, the *a-c* interval in the waves representing the first member of the radial group is 0·2 seconds, in the second 0·26 seconds. The third *a* wave is blocked.
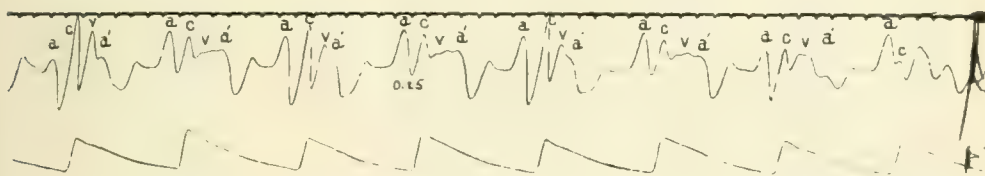
Fig. 2. Same as above, February the 10th, 1911. The rhythm is an incomplete block, the ratio being 2 : 1.

No records were taken from this time until February the 10th, 1911, the day of his fourth admission to the hospital. Jugular and radial curves made on this day show the presence of incomplete auriculo-ventricular block, the ratio being 2 : 1 (Fig. 2). There is no record as to whether the patient had taken digitalis before admission, but it is probable that he had. Curves made on the following day (Fig. 3 and 4)* and on February the 13th, 1911 (Fig. 5) showed that the incomplete block had given way to complete dissociation. The rate of the ventricular beats was 43·8 and of the auricular 82 (Fig. 3 and 4). The nature and the rhythm of the ventricular complexes were very unusual. The rhythm of the auricles was fairly regular. With certain exceptions, to be described, that of the ventricles was also regular. But the outline of the successive complexes changed so that no two were

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* The original curves are faint. They were photographed, and the photographs were reinforced. These were then bleached. The bleached overlined photographs are reproduced.
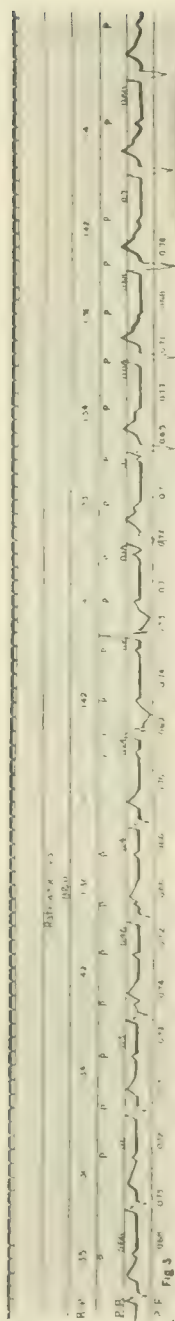
Fig. 3. Electrocardiogram, lead *II*, February the 11th, 1911. Complete auriculo-ventricular dissociation is shown. The auricular waves are practically equidistant. The ventricular complexes vary. Two complexes at the middle of the curve represent beats arising in the right side of the heart ; at the end in the left side. For further details, see text.
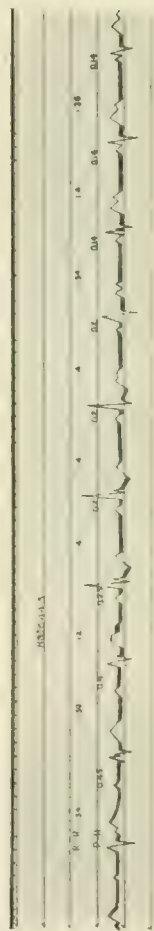
Fig. 4. Same as Fig. 3, except that the ventricular complexes at the end resemble those in the beginning.
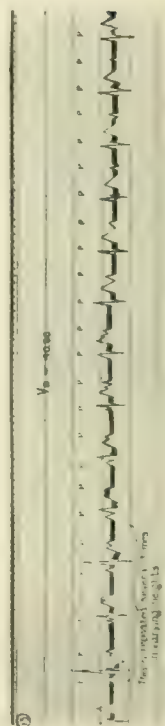
Fig. 5. Electrocardiogram, lead *II*, February the 13th, 1911. Shows rapidly changing forms of ventricular complexes.
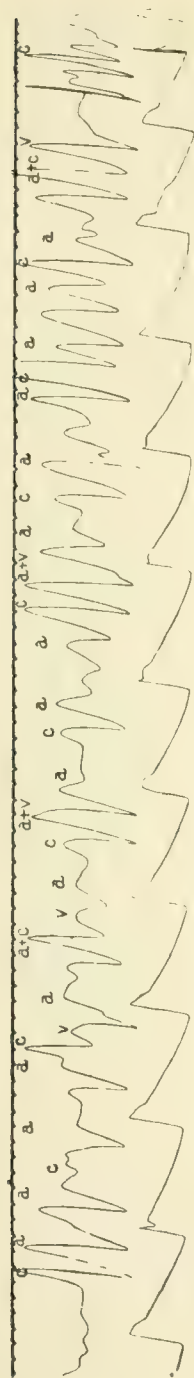
Fig. 6.   Polygraph curve, February the 17th, 1911.   Shows complete As-Vs dissociation.
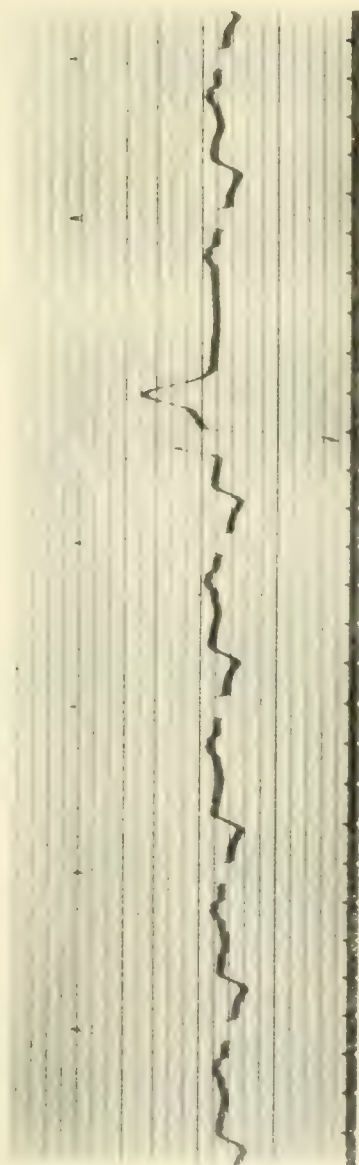
Fig. 7.   Electrocardiogram, lead II, February the 18th, 1913.   This curve is identical with those made December the 19th, 1911. It shows a normal sequential rhythm.   One premature beat arising in the left ventricle is seen.

TABLE I.

No of cycle	Curve 5			Curve 6			Curve 8, Figure 3				Curve 9			Curve 10				Curve 11				Curve 12, Figure 4			
	S-S	S-R	R-RR-S	S-S	S-R	R-RR-S	S-S	S-RR-R	R-RR-R	R-S	S-S	S-RR-R R-R-S		S-S	S-RR-R	R-RR-R	R-S	S-S	S-RR-R	R-R R-R	R-S	S-S	S-R R-R	S-R	R-S
1	1·43			1·36			1·35				1·36			1·4				1·38				1·34			
2	1·4			1·38			1·36				1·24			1·4				1·4				1·39			
3	1·44			1·38			1·34				1·4				1·28			1·4					1·2		
4	1·4			1·4			1·42				1·4					1·36		1·4						1·4	
5	1·43			1·4			1·36				1·4					1·44		1·4						1·4	
6	1·41			1·4				1·3			1·4			1·4			1·4	1·38						1·4	1·34
7	1·4			1·38					1·42		1·4							1·4				1·4			
8	1·4	1·36		1·38			1·33			1·41	1·32								1·28			1·36			
9				1·38			1·34				1·36							1·4		1·4					
10			1·43	1·4			1·36				1·4							1·4		1·4					
11			1·2	1·4			1·42				1·34							1·4		1·4					
12			1·4	1·38			1·4				1·38							1·38			1·4				
13			1·4	1·38							1·36							1·38			1·4				
14			1·4	1·4							1·38							1·4							
15			1·3	1·36														1·38							
16				1·36																					
Rate							Rate 43·8				Rate 4·5			Rate 43·8				Rate 42·5				Rate 44·5			

precisely alike. Two chief types may be distinguished among them. Some
resemble beats which respond to stimuli arising in the wall of the right,
and others to stimuli arising in the wall of the left ventricle. Beside this
fundamental difference between the groups, each group contains members
which differ slightly from each other. Gradual transitions between the
two groups can be recognised. At the time of transition from one group to
the other, a change in mechanism occurs, for the interval between the beats
is smaller than between beats of like nature (Table I). For example, in
Fig. 3, at the beginning of the curve, the interval between the beats in a
group of the same nature is between 1·34 and 1·36 seconds. When the nature
of the cycles changed, this interval is reduced to 1·3 seconds. The reduction
in time is even more strikingly shown in Fig. 4, where at the beginning of
the curve the interventricular interval is 1·34 and 1·39 seconds, and at the
time of transition 1·2 seconds. In these curves, and in others as well, the
transitions take place from cycles in which the most prominent wave is S
to cycles in which the R waves are most prominent. When the transition
is in the reverse direction, that is to say, from cycles in which the R waves
are large to those with prominent S waves, the interventricular intervals are
practically unchanged, or may be only slightly reduced (Fig. 3 and 4, and
Table I).

The phenomenon which has been described was shown characteristically
in all the curves made on February the 11th and on the succeeding days.
It persisted until a few days before the patient left the hospital, when, as
has been said, the sequence of chamber contraction was normal. It has
remained normal for two years (Fig. 7). An occasional premature ventricular
contraction has occurred, and one such is seen in the figure.

The intervals between ventricular cycles in a few selected curves are
given in Table I. Two of them have been reproduced, curve 8 as Fig. 3
and curve 12 as Fig. 4. In the first column, the numbers represent the
cycles. S-S represents the interval between cycles in which the S wave is
prominent ; S-R, the transition from cycles with a prominent S wave to
cycles with a prominent R wave ; R-R, the interval between cycles having
a prominent R wave ; R-S, transitions the reverse of that seen in S-R.

Discussion.

The irregularity which was detected and analysed on the third day after
the patient's admission to the hospital consisted, then, in lengthening of the
conduction time and blocking of the third auricular beat. This rhythm has
repeatedly been observed as the result of the administration of digitalis,
and may have been caused by the drug in this patient. The presence
of the irregularity on the day of admission was due in all likelihood
to his taking the drug before admission. On the fourth admission
(February the 10th), the incomplete block and the complete dissociation

were probably due to the same cause. This rhythm was present also on the 13th. From the 15th to the 22nd he was given digitalis, and on the 17th it was also present. Whether due to digitalis or not, the arrhythmia disappeared after the discontinuance of the drug.

Two explanations of the curious succession of differently shaped ventricular complexes seem possible. The first assumes a single permanent site in the main stem of the conduction system before its division into right and left branches as the source of stimulus production ; and this site is supposed to discharge impulses at regular intervals. Under this assumption the impulses are conducted now in one branch of the system and now in the other ; the varying ventricular complexes depending on which branch the impulse traverses. The passage of the impulse over one branch would, according to this interpretation, be the result of temporary functional depression in the other. The interventricular interval at the time of transition is shortened because recovery from depression permits acceleration of the rate of conduction of the impulse descending from the site in the A-V bundle where it is produced. But this explanation meets with a difficulty. It assumes that complete dissociation between the contractions of the auricles and of the ventricles may be present, as a result of a temporary derangement, probably toxic, of the conduction system. But the derangement must then be of such a nature that impulses could not be conducted from auricles to ventricles, but could be conducted over that portion of the system in continuity with the ventricles ; that is to say, the portion between the A-V node and the distribution to the ventricular muscle. A difference in the rate of conduction probably exists between different portions of the A-V system, as suggested by the experiments of Hering,[1] who states that of the various portions of the system, the node of Tawara (the A-V node) delays the passage of impulses most. If this is true, it may be assumed that causes which increase the delay in the propagation of impulses may increase it most at the A-V node, and may leave the rest of the system, that part between the node and the ventricles, less affected. Digitalis causes an impairment in conduction and may be assumed to do so principally at the node. The branches would then still be able to conduct impulses formed somewhere in the main stem, but not quite normally. Under these circumstances variation in the degree of depression in the two branches might occur and permit the change in the type of complexes which has been described.

The second explanation is that the site from which these impulses to contraction come is not fixed, but wanders from one side of the heart, that is to say of the conduction system, to the other. To this explanation there are objections. Impulses so widely scattered may give rise to an orderly succession of contractions, but such an occurrence is unlikely. The shortened intervals at the times of transition in the present curves also fail to support this explanation, for the orderly occurrence of shortening may be held to indicate the presence of a well-defined mechanism quite at variance with haphazard dislocations of impulse formation.

Another mechanism may be mentioned as a cause for varying ventricular complexes. Lewis[2] has shown that very definite changes in the ventricular complexes may occur in dogs' hearts when the stimuli to contraction arise synchronously, or almost synchronously, in the auricles and in the wall of the left ventricle. The second impulse in his experiments was due to a " rhythmical induction shock applied to the left margin of the heart " (Fig. 120). The ventricular complexes, as has been said, vary under these circumstances ; some of them, indeed, have an outline not unlike some found in the curves of this patient. But the existence of block in this patient makes it very unlikely that the interference between two competing stimuli (one being auricular) influenced the change in the ventricular complexes. Rothberger and Winterberg[1] have reproduced curves (Fig. 4, 9, 10, 11, 18) resembling these, except that the ventricular rhythm is irregular, and they consider that the variations in the ventricular complexes are due either to a single site or to several competing sites of stimulus production. Their curves were taken from dogs, and under conditions (injection of barium chloride and stimulation of the left accelerator nerve) of which we have no clinical parallel.

On the whole, the evidence favours an intoxication as the basic cause of the phenomenon of changing ventricular complexes, assuming that the patient under discussion had digitalis intoxication : this explanation is supported by the evidence of Rothberger and Winterberg's curves. Another case, yielding similar curves and reported by Oppenheimer and James,[3] also adds weight to this explanation. At autopsy, serial sections of the heart of their patient failed to show a lesion in the conduction system. The fact that complete restoration of the sequential beat took place in our patient is evidence that the phenomena observed resulted from a temporary intoxication rather than from an anatomical lesion in the conduction system.

SUMMARY.

A patient is described who showed during a period of six months almost continuous cardiac failure. During this period the rhythm of his heart-beat changed from one showing lengthened conduction time and incomplete heart-block to one of complete auriculo-ventricular dissociation. Over part of the time he took digitalis. On one occasion, during the stage of complete dissociation, the complexes representing ventricular contractions varied from beat to beat. This phenomenon was probably due to digitalis intoxication. He recovered from the condition completely and has been well for two years.

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A CASE OF ACUTE RHEUMATIC CARDITIS AND AURICULAR FIBRILLATION IN A CHILD.

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AND

CAREY F. COOMBS

(*Bristol*).

THE case recorded is one of intense cardiac inflammation in a child of 5 years, which proved fatal in six days. Reasons are given for regarding it as an extremely virulent example of rheumatic infection of the heart. A peculiar interest lies in the fact that total arrhythmia of the type associated with fibrillation of the auricles developed before death. Histological study of the cardiac tissues showed a widespread and intense focal inflammation of the myocardium, the cells of which were injured far more severely than is the rule in rheumatic carditis. These cellular lesions were unusually prominent in the auricular walls.

A boy of five years complained of slight sore throat and pain in the right knee and the left wrist on October the 13th. 1912. Both joints were found to be swollen and tender and his temperature was 102° F.. He was ordered fifteen grains of salicylate of soda every four hours. The child was seen again three days later. and the fever and arthritic pain were still present, while in addition the heart was found to be dilated. He was ordered twenty-five grains of salicylate of soda every four hours. Two days later the child became much worse. His face was dusky and vomiting set in. He was admitted to hospital. His previous health had been good. the only acute illness having been measles. There was no personal or family history of rheumatic fever. On admission on the fifth day of illness the boy looked extremely ill. The temperature was 102·8°, the pulse 140. and the respirations 60. Pain was complained of in the præcordial region and the right knee was swollen and tender. The face was somewhat cyanosed, the liver was enlarged. and venous pulsation was marked in the neck. Examination of the heart showed the presence of dilatation. the left border extending to one inch external to the left nipple and the right border half an inch to the right of the sternum. The pulse was markedly irregular. feeble. and of low tension. Polygraph tracings showed a gross type of pulse irregularity (Fig. 1), while

the venous tracing from the neck was of the ventricular type (Fig. 2), there being no trace of an auricular wave. The boy slept for an hour and a-half and then vomiting came on and was very persistent for some hours. During the night he was restless and in the morning the persistence of the vomiting was exhausting him so much that in order to relieve it an attempt was made to wash out the stomach ; but this was followed by sudden syncope. The total duration of the illness was six days.

At the necropsy on the day of his death there were no pathological changes apart from the points noted below. The lungs were congested. The pericardium contained no excess of fluid and presented no signs of inflammation, but small scattered hæmorrhages were seen both on the visceral and the parietal surfaces. The heart was slightly enlarged, owing
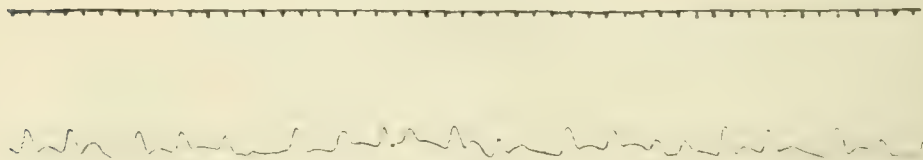
Fig. 1.
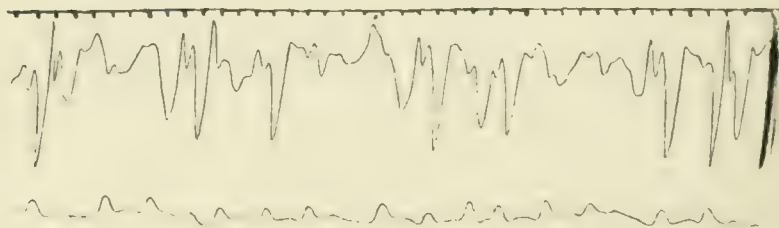
Fig. 2.

apparently to dilatation of the right auricle and ventricle. The wall appeared to be soft and flabby. There was a slight thickening on the edge of the mitral valve about the size of a pin's head. No other valvular changes were present. The liver was enlarged and congested, and on section showed many pale, fatty areas. The kidneys were congested and small hæmorrhages were present on the walls of the pelvis.

Through the courtesy of Dr. Perkins, Pathologist to the Paddington Green Children's Hospital, one of us (C. C.) was enabled to make a histological examination of various parts of the heart. In addition to sending us a number of blocks, Dr. Perkins also very kindly prepared for us a series of sections stained with Scharlach R for fat. A brief account of the results of this examination must now be given.

Myocardium. The muscle cells displayed a remarkably intense degree of fatty metamorphosis : large tracts in the wall of the left ventricle and in the interventricular septum were completely altered so that not a single normal cell could be found, many of the cells being converted wholesale into aggregations of fat. In the wall of the right ventricle the alteration was far less complete, but nevertheless patches of fatty metamorphosis were to be seen scattered here and there. In the auricular walls there was fatty change of a very unusual intensity, particularly in the right auricle. In the sections taken from this part of the cardiac musculature the whole thickness of the wall was altered, and scarcely a single cell was free from coarse aggregations of fat. In many cells the normal texture had entirely disappeared, the fat replacing all the usual features. In the left auricle and in the interauricular septum the alteration was less complete, though even here it reached a high pitch of intensity. Broadly speaking, there was a close coincidence between these changes and the inflammatory phenomena presently to be described ; where the reaction was most intense, there also the cells were most degenerate. In areas where the aggregation of fat was not so remarkable, many cells exhibited cloudy swelling, and pigmentation had occurred. The fibres of the auriculo-ventricular bundle appeared to be relatively free from these regressive changes.

The inflammatory reaction was extraordinarily wide-spread and intense. It reached its highest pitch in the wall of the left ventricle, the septum ventriculorum and the wall of the right ventricle being less severely injured. In the right auricle the reaction was very widely diffused, and less distinctly focal : it was almost as intense in the interauricular septum but distinctly less so in the wall of the left auricle. The auriculo-ventricular bundle (which, though not cut serially, was examined in sections from one large block, including its main stem) was diffusely infiltrated with endothelial leucocytes : these were most thickly gathered in the vessels lying in the connective tissue deep to the bundle, whence they spread into the bundle itself. The outer portion of the sino-auricular node alone was examined—that part which lies nearest to the right auricular appendix : it was more intensely attacked than the neighbouring portion of auricular musculature by a proliferative process producing endothelial leucocytes, new capillaries and some fibroblasts, but even so a considerable portion of the node as seen in transverse sections was untouched.

In the main the inflammatory reaction consisted of aggregations of " endothelial leucocytes," *i.e.*, cells endothelial in type arising apparently from proliferation of the cells lining the capillaries and lymphatics. These aggregations were not limited to the immediate neighbourhood of the blood-vessels, but radiated thence in fine granulations between the muscle fibres. In some spots the texture of these cells of endothelial origin was obscured by regressive changes. There were a few large foci in which polymorphonuclear leucocytes played an unusually prominent part ; in some, indeed, these

constituted the predominant feature of the reaction, and in such spots they were often necrotic and stained imperfectly. In these areas, which were in several instances associated with the profoundest degrees of vascular change described below, the muscle fibres had suffered most severely, being broken up and distorted as if by some gross physical injury. Even in these areas, however, a large proportion of endothelial leucocytes was discernible.

The vascular changes were most striking. At one end of the scale should be set swelling and proliferation of the endothelial cells in the smaller arterioles ; at the other end, thrombotic inflammation of quite large vessels, e.g., those running through the centre of a papillary muscle, leading to their total occlusion and to a marked perivascular leucocytosis. In the wall of the right auricle a large arteriole showed these changes. The other pheno- mena of vascular origin were the formation of groups of "endothelial leucocytes," i.e., cells thrown off by proliferation of the lining of the smallest blood vessels and the lymph channels ; wholesale construction of new capillaries, though the endothelial reaction did not appear to have attained to this stage except in certain areas ; and capillary hæmorrhages. Some parts of the myocardium, and particularly the wall of the left auricle, displayed a high degree of passive hyperæmia.

Endocardium. At the base of the mitral valve there was early proliferation of the endothelium covering its surface and lining its vessels.

Pericardium. No inflammatory changes were noted.

This case calls for comment especially in two directions.

A.—*Its relation to rheumatic infection.* We regard this case as rheumatic for the following reasons.

Clinical. Although the patient was under our observation only for the last twenty-four hours of life the clinical history of the illness and the conditions found on examination made a diagnosis of rheumatic fever fairly definite. Whatever view one may hold as to the effects of the large doses of salicylate of soda which had been taken, the cardiac condition was certainly not among them. The severity of the illness suggested the possibility of an acute septicæmia, but no evidence of any infection other than rheumatic could be detected either during life or after death.

Anatomical. On the anatomical side it was a pancarditis, *i.e.*, there were foci of inflammation scattered diffusely throughout the cardiac musculature, and the mitral valve also showed evidences of irritation. Microscopic

examination showed that the inflammatory reaction was pre-eminently formative in type, and that—as is characteristic of rheumatic lesions—the vascular endothelia figured prominently in this reaction.

The stages of the tissues' reply to irritation by the streptococcus rheumaticus would appear to be as follows. First, the endothelia of the smaller blood vessels and lymphatics proliferate : this is manifested in partial or complete occlusion of vessels with or without thrombosis, in the dissemination of " endothelial leucocytes " which are mainly collected in perivascular foci, and in the building up of new capillaries. Second, the perivascular connective tissues display a fibroblastic reaction, especially around the newly-formed capillaries. Third, leucocytes arrive in the disturbed area : in most areas the polymorphonuclears are represented but sparingly, but the more severe the attack the more likely they are to appear, and in some spots they even dominate the picture especially where large vessels are closed by inflammatory thrombosis. The usual appearances, therefore, are those of a blood-borne infection of a virulence so moderate that it is for the most part dealt with successfully by the first line of defence, the vascular endothelia.

In the case under consideration, these appearances, as seen in an early stage, were present ; the characteristic " submiliary nodule " had not had time to develop, but that which precedes it—endovascular proliferation with " endothelial leucocytosis "—was universally to be seen.

Bacteriological investigation by Dr. Perkins discovered the presence of a streptococcus in pure culture from the cerebro-spinal fluid. Grown at first on blood-agar this was subcultured into broth and injected into a rabbit. Unfortunately in subculture its virulence was lost and it had no pathogenic action on the rabbit. Dr. Perkins also made cultures from the right knee and the spleen but no organisms were found.

B. On these grounds, therefore, we are justified in regarding this as a case of rheumatic infection of the heart. Having established this we proceed to the next statement that the case was one of exceptional severity—a case of *fulminating cardiac rheumatism.* The disease ran an abnormally rapid course, six days only from start to finish ; and the histological changes were indicative of a much larger dose of infection than usual. Naming them in the order in which they occurred, the vascular injuries were more widespread and profound and affected vessels of a larger calibre than is usual : the reactive changes in the cardiac wall were spread over wider areas, the unusual abundance of polymorphonuclears also suggesting an irritation at longer range than is the rule in acute cardiac rheumatism ; and the muscle cells themselves were very much more severely damaged than is customary in this disease. The remarkable severity of the attack may perhaps be coupled with the unusually early age at which it occurred ; though one of us (C. C.) has

made histological examinations of hearts almost as intensely inflamed in subjects of maturer years. There is also a striking similarity between the lesions in this case and those of experimental rheumatism, in respect of the profound vascular injuries and the unusual abundance of polymorphonuclear leucocytes.

A METHOD OF MEASURING THE RATE OF TRANSMISSION OF THE CONTRACTION WAVE IN THE DOG'S AURICLE.

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METHOD.

In a previous article.[1] I described some experiments upon the right auricular appendage of the dog's heart, in which the tissues at the base of that organ were crushed in such a manner that a narrow bridge of muscle remained and joined the appendage and the chief mass of auricular tissue. It occurred to me that a similar preparation might be utilised to test the rate of propagation of the contraction wave in the dog's auricle. In the experiments, conducted under full anæsthesia with morphia, paraldehyde and ether, the tissues are crushed in a single line running from the auriculo-ventricular groove, at the insertion of the base of the right auricular appendage, towards the head of the sino-auricular node or a little to the appendage side of it. In this manner the appendage is separated, physiologically but not anatomically, from the auricle, except for a bridge of connecting tissue of 3 or 4 millimetres breadth. This bridge lies at the angle between the appendage and superior vena cava, and is left in this region because a large arterial twig runs into the appendage from the main sino-auricular artery near the angle. The position of the arterial twig is subsequently confirmed by microscopic sections cut across the bridge. After the completion of the crush two pairs of small fishhook electrodes are secured, one (A) at the tip of the appendage, the other (B) at the bridge. The auricular appendage, subsequent to this manipulation, maintains its activity and normal colour in favourable experiments ; the results obtained in such experiments are accepted.

The rate of propagation is measured in the appendage in a manner similar to that employed in estimating the rate of propagation of the excitation wave in nerve. A series of rhythmic induction shocks is thrown into the electrodes A and B alternately and at such a rate that the series of excitations dominates the movements of the whole heart. The excitations are signalled and records of the heart's contractions are obtained galvanometrically

(lead *II* being employed). An appreciable interval elapses between a given signal of stimulation and the corresponding summit *P* of the electrocardiogram. The difference between the intervals, the stimulation being now through electrode *A* and now through electrode *B*, is taken as a measure of the time occupied by the contraction wave in traversing the measured distance between the electrodes.

The electrocardiogram does not change materially when the site of stimulation is altered, for the paths of the contraction wave, once it has traversed the bridge, are practically constant (the tissues are crushed with this object in view) and the currents developed in the appendage itself, now contracting one way and now the other, are practically without influence.

The movements of the signal and galvanometric string are photographed upon the same plate. The time marker, a modification of that devised by Bull, consists of a rotating toothed disc ; the light from the projecting system is occluded at each ·04 second by a tooth, each fifth tooth being broader than those which intervene. The time is thus marked in lines across the plate, in the line of the camera lens : the twenty-fifths by thin and the fifths by thicker lines.
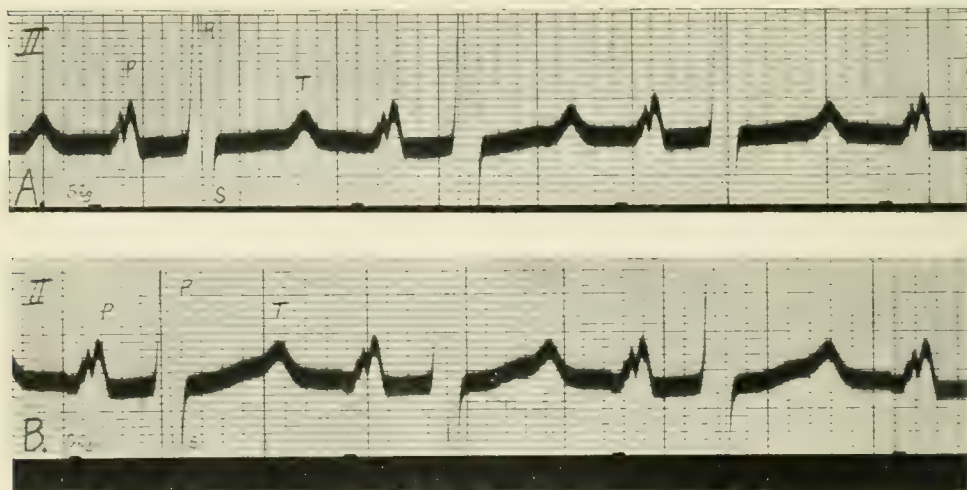
Two electrocardiograms from a dog. The heart is responding to rhythmic induction shocks applied (*A*) at the tip of the appendage , and (*B*) at the bridge. The signal of stimulation is seen below in each instance. The time-marker, which rules vertical lines, represents one-fifth and one-twenty-fifth of a second.

Measurements from actual experiments are given in the accompanying table ; the measurements were made upon the Lucas microscopic comparator,[2] kindly lent to me by Dr. Keith Lucas for the purpose.

Dog		Signal to P summit in Secs.	Averages.	Difference in secs.	Length muscle strip in mm.	Conduction rate, mm. per sec.	Heart rate per minute.
DO	Append. stim Bridge stim.	·0416, ·0429, ·0403 = ·0280, ·0252, ·0266	·0416 ·0266				219·0 218·8
				·0150	19	1266	
DQ	Append. stim. Bridge stim.	·0450, ·0450, ·0420 = ·0180, ·0210, ·0210 =	·0440 ·0200				111·1 110·8
				·0240	20	833	
DR	Append. stim. Bridge stim.	·0352, ·0336, ·0368 = ·0135, ·0128, ·0176 =	·0352 ·0146				203·8 202·7
				·0206	22	1067	
DP	Append. stim. Bridge stim.	·0598, ·0598, ·0684 = ·0195, ·0168, ·0156 =	·0626 ·0173				153·0 153·0
				·0453	29	640	
DP	Append. stim. Bridge stim.	·0829, ·0806, ·0650 = ·0351, ·0377, ·0223 =	·0761 ·0317				201·0 201·6
				·0444	29	653	

This instrument is more than sufficiently accurate for the readings : of possible sources of error in measurement the greatest is in the choice of the point at which the cross lines of the microscope shall fall upon the electrocardiogram, namely, the selection of the point at which P commences. The error is not large, amounting at the most in suitable curves to ·003 sec. ; the greatest possible error in the conduction rate as calculated from the varying measurements is in a single instance as much as $37^{\circ}/_{0}$, but as a rule it is from $7^{\circ}/_{0}$ to $15^{\circ}/_{0}$, and therefore comparatively trifling. The length of the muscle strip is measured by means of dividers while the heart still beats, the length taken being that between the centres of the electrodes when *the muscle is in the full diastolic position.*

As may be seen from the tabulated results the rate of conduction in the dog's auricle is variable, the slowest rate of propagation being 640 mm. per second, the most rapid 1.266 mm. per second, in this series. The rate varies approximately from $\frac{1}{2}$ to 1 metre per second.

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A POLYGRAPHIC STUDY OF FOUR CASES OF DIPHTHERIA, WITH A PATHOLOGICAL EXAMINATION OF THREE CASES.*

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In the following pages the disorders of the cardiac mechanism which were encountered in a polygraphic study of four cases of severe diphtheria are described. Three of them were fatal and in each case the heart was subjected to a minute examination of all parts, and an account of the results of this examination is given.

In the fourth case an attack of paroxysmal tachycardia was recorded, and as this condition is infrequent in diphtheria it has seemed expedient to include it in the present series.

Although the varieties of arrhythmia which were recorded in these four cases were numerous there were certain types which were common to all. Some were such as are of common occurrence in other diseases, namely, auricular extrasystoles and heart-block ; others again were exceptional in this or in other diseases, and of this group a rhythm which is thought to be generated in the region of the auriculo-ventricular node (nodal rhythm) ranks as the most important.

In each case a brief clinical history will be first given, then the polygraphic tracings will be recorded and discussed, and thirdly the results of the post-mortem examination will be illustrated. After the cases have been described in their polygraphic and pathological aspects, their relationship with certain instances of cardiac irregularity in diphtheria which have been already published will be discussed.

CASE 1.

Clinical History of CASE 1.

Female, aged 7 years, was admitted on October the 17th, 1912, which was the fourth day of illness.

On October the 14th the child had vomited and complained of pain on swallowing food. The doctor in attendance took a swab from the throat, and on receiving a positive report sent the child to the fever hospital.

On admission on October the 17th, there was an extensive, thick membrane on both tonsils, and 6,000 units of antitoxin were administered. The temperature was 100·6 and the pulse rate 126. The area of cardiac dulness and the position of the apex beat were normal, and the heart sounds were clear.

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* The subject matter of this paper was presented as a Thesis (M.D.) in the University of Cambridge.

On the next day, the fifth day of illness, 4,000 units of antitoxin were administered although large pieces of membrane were separating and the throat was cleaner. The temperature was 100° and the pulse rate 104. The apex of the heart was displaced to the nipple line, and on auscultation the first sound was poor and the second sound was reduplicated. There was a trace of albumen in the urine.

On the sixth day of illness there was still a large piece of membrane on the right tonsil, extending to the soft palate. The temperature was 99·4 and the pulse rate 106. There was no albumen in the urine.

On the seventh day of illness the temperature fell to subnormal at night and the child vomited. On October the 21st, the eighth day of illness, the heart condition was the same and the pulse, though regular, was of low tension. The pulse rate was 92.

From the fifth to the eighth days, normal jugular and radial tracings were obtained.

On October the 22nd, the ninth day of illness, there was a marked serum rash and the pulse was occasionally irregular. Jugular tracings obtained on this day demonstrated the irregularity to be due to auricular extrasystoles. The throat was cleaner, the temperature was normal and the pulse rate 94. The next day nasal phonation was noticed and there was a tendency towards the regurgitation of food. The first sound of the heart was faint and approximated a second sound in character. There was occasional vomiting and there were evident signs of collapse. On this day tracings were obtained which showed the presence of a nodal rhythm.

On October the 24th, the eleventh day of illness, the temperature was 97·4° and the pulse rate 98, and a nodal rhythm was again recorded. The child was listless and apathetic, and occasionally vomited. The next day the extremities were cold and there was marked apathy and pallor. Tracings obtained from the jugular vein and radial artery demonstrated a rapid regular contraction of the auricles, accompanied by a slower ventricular rate, i.e., auricular flutter. The pulse rate varied between 90 and 102, and the temperature was subnormal.

On October the 26th, the thirteenth day of illness, the pulse rate was about 110 and normal polygraphic curves, infrequently interrupted by auricular extrasystoles, were obtained. On October the 27th, the child was restless, and as the radial pulse was imperceptible it was impossible to obtain either venous or arterial curves.

The next day, the fifteenth day of illness, the child died.

Polygraphic curves of CASE 1.

On October the 22nd, the ninth day of illness, the first irregularity was discovered. From Fig. 1 it will be seen that a normal rhythm is interrupted by auricular extrasystoles.

At x in Fig. 1 a premature beat appears in the radial curve which by measurement is found to correspond with an early c wave in the jugular curve. Preceding the c wave is a large wave which is composed of the v wave of the previous cycle and the a wave of the premature beat. That the premature contraction has originated in auricular rather than ventricular musculature is made certain by a consideration of the following facts. The time occupied by the systole and diastole of the premature beat and the cycle immediately preceding it is less than that occupied by two normal cycles : in other words, the compensatory pause is not complete. Secondly, certain characteristic variations in the length of the a-c interval are known to accompany premature contractions of the auricle and are present in this instance. The a-c interval of the premature cycle is longer than those which have preceded it, because the early auricular impulse finds the conductivity of the A-V bundle to some extent depressed : also, the a-c interval of the cycle following the premature contraction is shorter than usual, because the A-V tissues have had a longer period in which to recuperate.

The next day, October the 23rd, the tracing represented by Fig. 2 was obtained. In this figure there are two waves in each cardiac cycle in the jugular curve and they both fall within the period of ventricular systole,
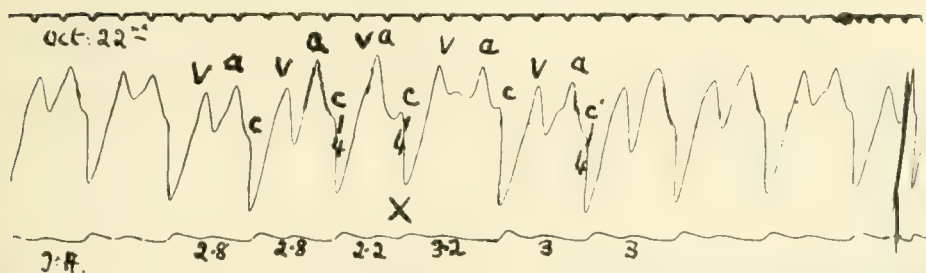
Fig. 1. Jugular and radial curves from *CASE* 1. At the fifth cycle (reading from left to right) at mark *x* a premature contraction of the auricle has occurred, and the *a* wave of the premature beat has fused with the *c* wave of the preceding cycle.
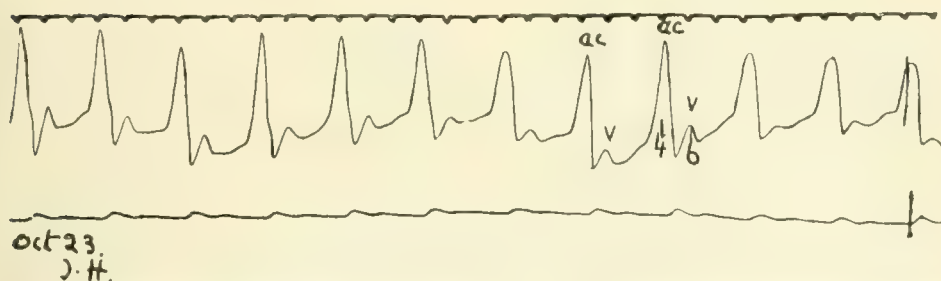
Fig. 2. Jugular and radial curves from *CASE* 1. In the jugular curve there are two waves, *i.e.*, *ac* which represents simultaneous contraction of auricle and ventricle and a smaller *v* wave.

and during the period of ventricular diastole no wave indicative of a separate auricular systole is to be found. It is apparent that the large waves of the last two cycles have broader tops than the previous waves, and in other tracings the wave broadens still further until two separate waves appear. The transition is at one time from a single to a double wave, and at another time from a double to a single wave. Such a transition from a double wave to a single wave is seen in Fig. 3. In this figure the jugular curve at the first cycle shows a double wave *c-a*, and the interval between these two separate waves is gradually shortened until at the ninth cycle there is a single sharp topped wave. The eleventh, twelfth and thirteenth cycles are again represented by slightly broader waves and at the fourteenth cycle a single wave is seen. The single wave persisted for three minutes and was succeeded by a gradual broadening into two waves.

For long periods there were only two waves which were separated by a considerable interval, and an example is shown in Fig. 4. Considerable lengths of tracings obtained on October the 24th from this case (*CASE* 1) showed the characters which are represented in Fig. 2-4, though the rhythm was occasionally interrupted by premature beats and the jugular curve then became more complicated. We must, however, consider the interpretation
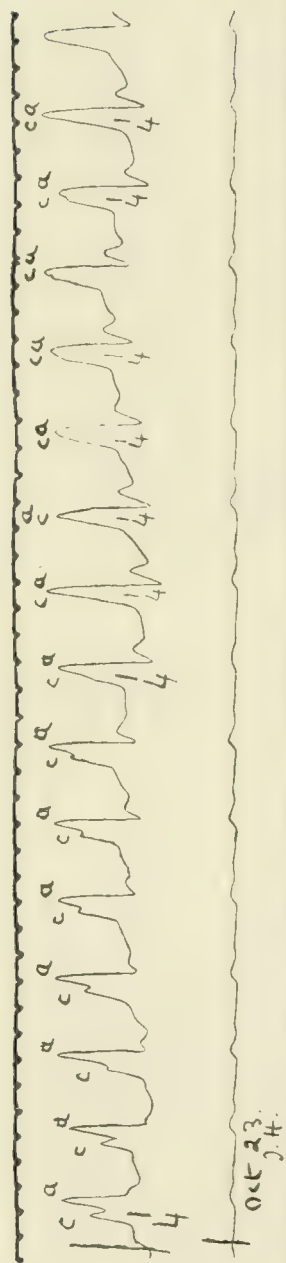
Fig. 3. Jugular and radial curves from CASE 1. At the first cycle there is a double wave c-a and at the ninth cycle there is a single large wave ca.
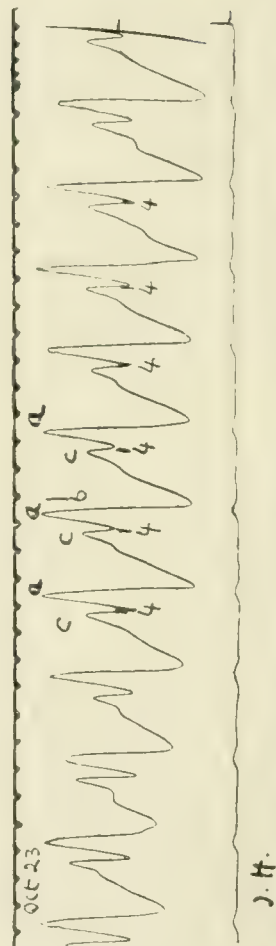
Fig. 4. Jugular and radial curves from CASE 1. In the jugular curve each cycle is represented by two waves c and a. Both fall within the period of ventricular systole. At the sixth cycle the markings 6 indicate the end of ventricular systole.

of the underlying rhythm before the variations are illustrated, and such an unusual rhythm demands a full discussion of its causation.

The most obvious feature in all three venous curves is the absence of an *a* wave in its normal position ; when two waves occur, they both fall within the period of ventricular systole. It is well known that venous curves can be divided into two chief classes, one class in which the contraction of the auricle causes a distinct wave during the diastole of the ventricle, the auricular form of venous pulse ; and the other, in which the auricular wave is absent in this position and there is only a ventricular systolic rise of pressure, the ventricular form of venous pulse. The latter type usually indicates the presence of auricular fibrillation and the pulse is completely irregular, unless there is complete dissociation of auricles and ventricles. Applying this consideration to the tracings under discussion we must conclude either that the auricles have ceased to beat co-ordinately and are in a condition of fibrillation, or that the auricular wave falls during the period of ventricular systole. If fibrillation of the auricles is present the regularity of the pulse necessitates the conclusion that there is auriculo-ventricular dissociation. The rapidity of the ventricular rate makes it improbable that the ventricle is responsible for its own stimulus formation. Further, this view would in no way account for the transition of one wave into two waves, and *vice versa*, an alteration which is characteristic of these three venous curves.

We are forced to the conclusion then that the auricular wave falls within the period of ventricular systole, and the types of arrhythmia in which this coincidence occurs must be discussed.

(1) In the first place, in certain instances of complete heart-block with dissociation of auricles and ventricles, the speed of both chambers may be so equal that waves due to auricular contraction may coincide with waves due to ventricular contraction. This synchrony, however, is usually very evanescent and is only present for two or three cycles, and separate waves soon make their appearance. Such uniformity of auricular and ventricular rates as occurred in this case has never been observed for such long periods in complete dissociation of the auricles and ventricles.

(2) In the second place, it may be that the auricular wave of one cycle is included in the ventricular period of the preceding cycle owing to marked impairment of conductivity in the *A-V* junctional tissues. With this interpretation the *a-c* interval would vary between 2·5-fifths of a second and three-fifths of a second. If the conductivity were so impaired it might have been expected that an occasional auricular beat would fail to reach the ventricle ; instead of this being the case later figures (Fig. 5-8) will show that at times auricular impulses pass readily across the junctional tissues to the ventricle. It is unlikely that the functional capacity of the junctional tissues would exhibit such a wide degree of variation within a moment of time.

The only remaining alternative seems to be that the auricles and ventricles are contracting in simultaneous response to a common impulse. This view, of course, presumes that there is an area of stimulus formation lying in the A-V node or bundle. In Fig. 2 the auricles and ventricles would appear to contract simultaneously and give rise to a large single wave ac. In Fig. 4 there is a tendency for the auricular contraction to follow the ventricular contraction at a uniform interval of time. This discrepancy in the time of appearance of auricular contraction can be due to one of two factors : either the stimulating focus is not constant, at one time being lower in the A-V nodal and junctional tissues and giving rise to the later appearances of the auricular systole, or the capability of the auricle to receive stimuli from a constant stimulating focus is not uniform. It seems impossible to decide which alternative is the correct explanation. From the foregoing considerations it seems highly probable that for long periods the auriculoventricular nodal tissues usurped the function of pacemaker of the heart in this case. (CASE 1.)

Although the characters which are shown in these figures were present throughout considerable lengths of tracing, periods occurred when these comparatively simple forms were complicated by the appearance of premature contractions which originated in both auricles and ventricles. Such an interruption of the nodal rhythm is seen in Fig. 5. It will be seen in this figure that a premature contraction of the auricle occurs at the seventh cycle, and that in the eighth cycle the auricles and ventricles contract synchronously. At the ninth cycle the auricular slightly precedes the ventricular contraction, and thereafter the original rhythm is re-established. The premature contraction of the auricle may be an " escape " from the sino-auricular node which forestalls the nodal impulse. The ventricle responds to the nodal impulse but the auricle, still contracting, is unable to do so. For two cycles the auricle responds more readily to the nodal stimulus and then the original rhythm is restored. The above seems to be the probable explanation of the irregularity, as subsequent figures seem to indicate the liability of impulses from the sino-auricular nodal tissues to disturb the steadiness of the nodal rhythm. Thus in Fig. 6 a normal sinus contraction of the auricle is accompanied by a normal ventricular response.

At the fifth cycle (reading from right to left) an early auricular impulse disturbs the hitherto regular ca sequence.   This is followed by a normal sinus contraction and is indicated in the figure as such (a^1cv). It is presumed that the second auricular impulse occurs so shortly after the first premature beat that it forestalls the nodal beat and by passing an impulse on to the ventricle the nodal stimulus matter is destroyed. Though the irregularity which was imposed upon this regular nodal rhythm was usually due to premature auricular contractions, very rarely a premature ventricular contraction occurred.

In Fig. 7, the seventh cycle of the venous curve (reading from right to left) is composed of a premature auricular contraction and a ventricular
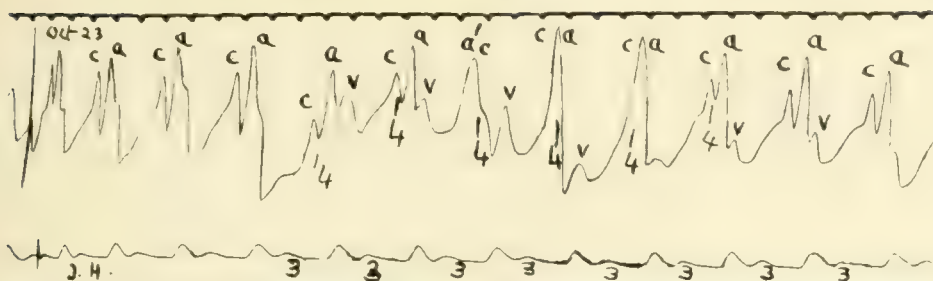
Fig. 5. Jugular and radial curves from *CASE* I. At the seventh cycle (reading from left to right) an auricular contraction (a¹) precedes the ventricular contraction, and after two simultaneous auricular and ventricular contractions the original rhythm is re-established.
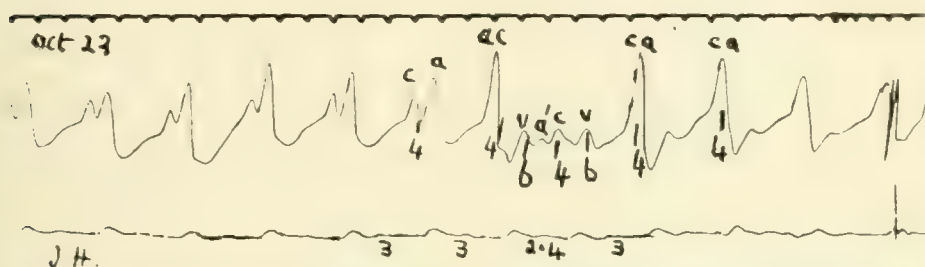
Fig. 6. Jugular and radial curves from *CASE* I. At the fifth cycle (reading from right to left) a premature auricular impulse occurs, followed by a sinus sequence (a¹cv).
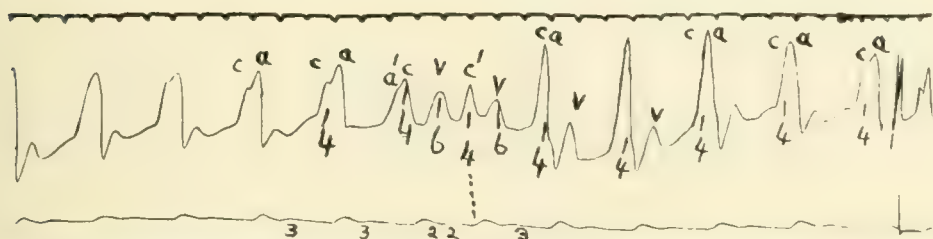
Fig. 7. Jugular and radial curves from *CASE* I. At the seventh cycle (reading from right to left) a premature auricular contraction occurs, followed in the next cycle by a premature ventricular contraction.

wave which has been caused by a contraction determined in the nodal tissues. In the next cycle a premature contraction of the ventricle (c^1) has occurred and no auricular contraction appears until the next nodal beat.

The frequent appearance of both auricular and ventricular extrasystoles made some of the jugular curves very complicated. One of the most complicated curves is shown in Fig. 8. If the tracing is followed in Fig. 8 from left to right from ordinate 1, there are two cycles in which the auricular wave follows the ventricular wave. In the third cycle there occurs a ventricular extrasystole and this is followed by an apparently normal sinus sequence.
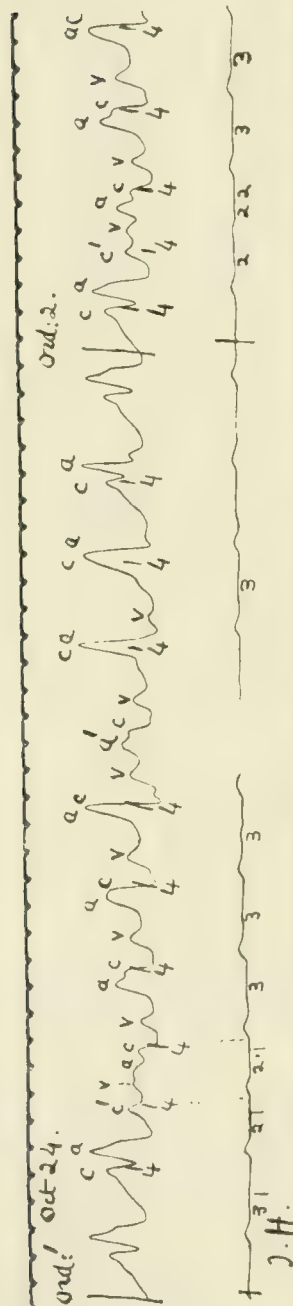
Fig. 8. Jugular and radial curves from CASE 1. To the right of ordinate 1, two ca sequences are followed by a premature ventricular beat (v-r). Then follow five cycles in which auricular precede ventricular contractions; thereafter the nodal rhythm is re-established. To the right of ordinate 2, a similar sequence of events is pursued.

At the fifth cycle the interval between auricular and ventricular contractions is shortened until at the seventh cycle there appears to be a nodal beat. Then follows an apparent sinus contraction and thereafter the nodal rhythm is re-established. To the right of ordinate 2, more or less the same sequence of events is portrayed. From this figure it would appear that there is a struggle taking place between the normal pacemaker of the heart (*S-A* node) and the new pacemaker (*A-V* node). This is the only interpretation which will account for the appearance of normal sinus sequences such as occur at the fourth and eighth cycles to the right of ordinate 1, and at the third cycle to the right of ordinate 2.
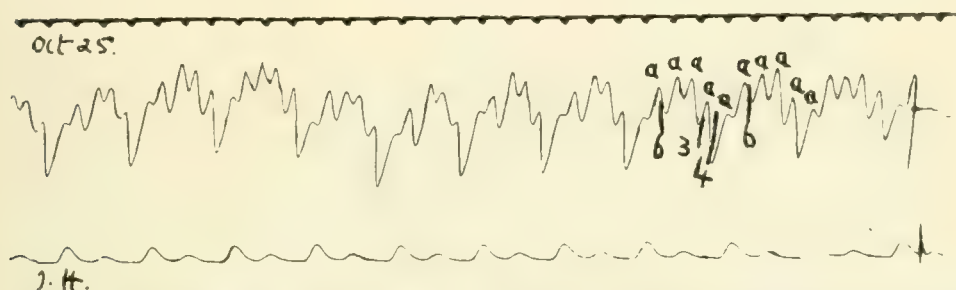
Fig. 9. Jugular and radial curves from *CASE* 1. It is thought that all the small waves in the venous curve represent contractions of the auricle and are marked *a*.
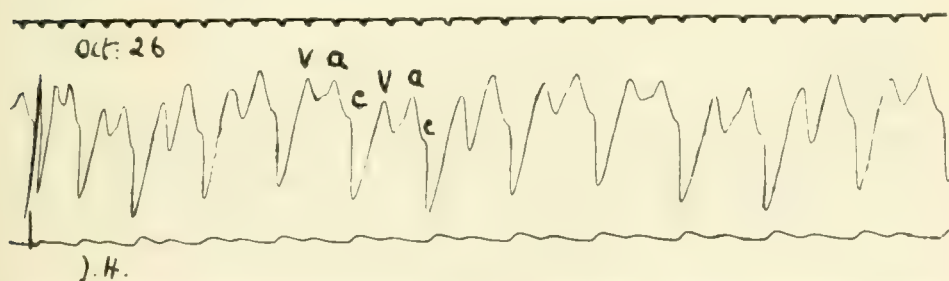
Fig. 10. Jugular and radial curves from *CASE* 1. The normal waves, *a*, *c*, and *v*, are present.

This form of irregularity was present throughout October the 24th, but the next day it gave place to an irregularity, the characteristics of which are represented in Fig. 9. In each cardiac cycle of the jugular curve there are five small waves which are regular and co-ordinate. It would seem that in this curve we are either dealing with a normal venous curve, with the addition of an unusual wave or waves, or that each single small wave represents a co-ordinate contraction of the auricles—auricular flutter. In each cardiac cycle during the systolic period (between 3 and 6) the waves might conform to those waves which form a normal venous curve, or each

wave again may be representative of a single auricular contraction. During
the period of ventricular diastole, that is in the period between 6 and 3,
there are two separate waves which must be caused by auricular systoles.
The regularity with which these small waves appear makes it probable that
they all have a common cause, and it is suggested that the auricles are
contracting regularly at a rate of about 500 per minute. Pressure upon the
vagus in the neck might have decided the point at issue, by causing inhibition
of the ventricle, while by this means the evidences of auricular activity
would have been undisturbed. It was not thought justifiable, however,
to attempt this procedure in a child who was so extremely ill. The next
day, though the child was evidently dying, the rhythm of the heart became
normal and Fig. 10 represents this condition.

Post-mortem examination of CASE 1.

A post-mortem examination was made on the day of death. On
opening the thorax pleural effusions were found with partial collapse of
both lungs, in which there were evident patches of early broncho-pneumonia.
The liver was fatty. The kidneys were pale ; the cortex was enlarged and
microscopically there were evidences of an acute nephritis. The heart was
pale and flabby, and had the " boiled " appearance of advanced cloudy
swelling. On opening the heart the valves were found to be normal. The
heart muscle was pale and friable, and in places had a yellow tint.

The following pieces were removed from the heart for microscopic
examination :—

(1) The region of the auriculo-ventricular node and bundle ; (2) Pieces
of ventricular muscle ; (3) A piece of auricular muscle.

(1) Serial sections were cut of the block containing the auriculo-
ventricular node and bundle from above downwards, and were stained with
hæmatoxilin and van Gieson's stain. Nearly every section was mounted
and examined. In section 424 the node was well seen and appeared normal.
The node was continued into the main stem of the auriculo-ventricular
bundle and was present in the following hundred sections. Unfortunately
the block of tissue had not been removed sufficiently far forwards and the
division of the bundle into its two branches was not found. The bundle
was followed until it appeared on the left side of the pars membranacea
septi and had the shape of a goose's head. Throughout its extent the fibres
were well formed and seemed to be perfectly normal. There was perhaps
a slight increase of vascularity and engorgement of capillaries. There was
no inflammatory exudate.

(2) (*a*) Pieces of ventricular muscle were stained with hæmatoxilin
and van Gieson's stain. In some parts of the ventricular muscle there
was a gross degree of interstitial myocarditis. In such areas the capillaries

were engorged and there was an infiltration of mononuclear cells of the formative type. The muscle fibres were granular and degenerated.

(*b*) Pieces of ventricular muscle were stained with hæmatoxilin and Sudan III. The muscle fibres were seen to be occupied by large and small droplets of fat, some of the fibres being more affected than others. Fatty degeneration was present throughout the ventricular muscle of both right and left chambers.

(3) The auricular muscle was the seat of fatty degeneration, though to a considerably less degree than was present in the ventricular muscle.

CASE 2.

Clinical history of CASE 2.

A male, aged 7 years, was suddenly seized with sickness and vomiting followed by difficulty in swallowing on October the 28th. On November the 1st, Klebs-Loeffler Bacilli were obtained from a throat swab, and 8,000 units of antitoxin were administered.

The next day, the sixth day of illness, he was admitted to the hospital. Patches of membrane were to be seen on both tonsils and there was a blood-stained discharge from the nose. The temperature was 98° and the pulse rate 90. There was no albumen in the urine. On examination of the heart the apex beat was under the fourth rib internal to the nipple line. The area of cardiac dulness was normal and the heart sounds were clear. On November the 3rd a profuse epistaxis occurred and a purpuric rash appeared on the neck ; the temperature was 97° and the pulse rate 100. The apex of the heart was slightly displaced outwards and the first sound had the abrupt character of a second sound.

On November the 4th, the eighth day of illness, the child was very quiet and more comfortable.

Polygraphic tracings taken on November 3rd and 4th showed that the rhythm of the heart was normal. On November the 5th there was a second epistaxis. On this day it was noticed that premature beats occurred while the heart was being examined by the stethoscope. No record was made of them. On November the 6th, the tenth day of illness, vomiting was frequent and there were conspicuous signs of collapse. The temperature was 97·4° and the pulse rate 94. On this day a nodal rhythm was shown to be present. The apex was in the nipple line and an occasional systolic murmur accompanied a feeble first sound. Albumen appeared in the urine for the first time on November the 7th. On the two following days, November the 8th and 9th collapse was extreme and vomiting was frequent. The heart sounds were very faint, and jugular and radial tracings demonstrated the presence of a 2 : 1 heart block. The pulse rate varied between 97 and 94. On November the 10th the child died.

Polygraphic curves of CASE 2.

Polygraphic tracings of *CASE* 2 up to the eighth day of illness showed that the rhythm of the heart was normal, and Fig. 11 is a tracing taken on November the 4th, the eighth day of illness.

Two days afterwards curves represented by Fig. 12 were obtained. In Fig. 12 there are two waves in each cycle of the jugular curve. The second wave occurs at a later period than did the second wave in similar tracings from *CASE* 1. (See Fig. 4.) Therefore, the second wave may be a *v* wave alone, and in that case the synchronous contraction of the auricles and ventricles gives rise to the first wave. On the other hand, the auricular may follow the ventricular contraction as seen in Fig. 3 and 4.

Fig. 11.   Jugular and radial curves from *CASE* 2.   A normal *a c v* sequence is figured.

Fig. 12.   Jugular and radial curves from *CASE* 2.   Each venous cycle is occupied by two waves marked *c* and *av* in three instances and *ca* and *v* in three instances.

Fig. 13.   Jugular and radial curves from *CASE* 2.   A diagram is interposed showing the relationship between auricular and ventricular systole.   Every alternate auricular impulse is blocked.

and the *a* wave is then fused with the *v* wave in the second large wave. Whichever is the correct interpretation it is probable that the stimulus to contraction springs from the nodal tissues.

On November the 8th, the twelfth day of illness, the nodal rhythm was replaced by a 2 : 1 heart block, polygraphic curves of which are seen in Fig. 13. By analysing this tracing it will be seen that the *a-c* interval is ·25 second in those periods in which auricular contractions are followed by ventricular contractions, and that the auricular rate is 180 and the ventricular rate is 90.

Post-mortem examination of CASE 2.

A post-mortem examination was made on November the 11th. On opening the thorax a small amount of fluid was found in the right pleural cavity. The lungs were congested and there were patches of early broncho-pneumonia throughout both lungs. There was some fluid in the pericardial sac and some recent lymph on the visceral pericardium. The heart was flabby and pale in appearance. On opening the heart the cavities were dilated though the valves were normal. The heart muscle was friable and very pale. The liver was fatty. The kidneys showed evidences of an acute toxic nephritis.

The following pieces were removed for microscopical examination : –

1. A portion of tissue at the junction of the superior vena cava and the right auricle which included the sulcus terminalis, the adjoining parts of the right auricle and right auricular appendix, and a part of the vena cava itself.

2. A block of tissue which included the auriculo-ventricular node, the auriculo-ventricular bundle and its two main branches. The posterior margin of this block extended to the opening of the coronary sinus and upwards to a distance of about 1 cm. beyond the pars membranacea septi. The upper limit of the block extended about 2 cm. above the auriculo-ventricular groove on the right side of the heart. The lower limit extended about the same distance below the auriculo-ventricular groove.

3. Portions of the walls of the right and left auricles.

4. Two or three blocks were removed from the interventricular septum and the right and left walls of the ventricles.

1. *The region of the sino-auricular node.* The block containing the sino-auricular node was embedded in paraffin and was cut at right angles to the lumen of the superior vena cava.

Nearly every section was kept and stained with iron hæmatoxilin and van Gieson's stain. The node was found to be well formed and was present throughout 124 sections. The artery of supply was prominent and eccentric. The nodal tissue was composed of an interlacement of fine muscle fibres and fibrous tissue, and throughout the node pathological changes were found ; the fine muscle fibres were granular and in many places fragmented ; the capillaries were dilated and engorged with red blood corpuscles, whilst free red cells and mononuclear cells could be discovered amongst the muscle fibres. The sino-auricular node was the seat of an acute inflammation.

2. *The auriculo-ventricular node and bundle.* This block of tissue was embedded in paraffin and serial sections were cut from above downwards. Nearly all sections were kept and stained with van Gieson's stain. In this case the bundle was found in about 400 sections. The bundle was small

and for the most part was found in a very thin pars membranacea septi. The fibres were well formed and beyond some slight capillary engorgement no abnormality in structure could be detected.

3   *The auricular muscle*, stained with hæmatoxilin and Sudan III, was found to contain a small amount of fat, similar to the condition of that described in the first case.

4.   *The ventricular muscle*, stained with iron hæmatoxilin and van Gieson's stain, and with hæmatoxilin and Sudan III, revealed no interstitial myocarditis, but was the seat of an intense fatty degeneration.

CASE 3.

Clinical history of CASE 3.

Child aged 5 years, was admitted on November the 12th.   He had been ill for two days with vomiting and pain on swallowing food.   On admission there was a thick septic membrane on the right tonsil extending to the uvula and soft palate, which gave to the breath a foul odour.   The temperature was 99·8 and the pulse rate 110.   6,000 units of antitoxin were administered, and the temperature was 97 and the pulse rate 120.   The apex of the heart was within the nipple line and the second sound was occasionally reduplicated.

The next day, November the 13th, the temperature fell to 96·6° at night and the pulse rate was 120.   On this day there was a faint trace of albumen in the urine.   On November the 14th, the fifth day of illness, the temperature was 97° and the pulse rate 112.   Polygraphic curves taken on this day showed that the rhythm was normal.

On November the 15th vomiting began and there were signs of collapse.   On November the 16th, the seventh day of illness, premature beats were detected by stethoscopic examination. It is thought that they were probably of auricular origin though no records were obtained.   The first sound of the heart was muffled and the apex was found to be in the nipple line.   The temperature was 97·4° and the pulse rate 92.

The next day, November the 17th, the heart sounds had a " tick-tack " character and the pulse rate was 68.   By polygraphic curves a nodal rhythm was shown to be present.   On November the 18th, the ninth day of illness, the temperature which had been submormal rose to 99·6° and the pulse-rate was 100.   The next day, November the 19th, there was frequent vomiting and also signs of collapse.   On November the 18th and 19th polygraphic tracings showed that the nodal rhythm was persisting.   On November the 20th, the eleventh day of illness, the pulse rate varied considerably in frequency, the extreme rates being 96 and 132. Polygraphic curves taken on this day are thought to indicate auricular flutter.   The temperature was 99·4° and pleural friction was detected at both pulmonary bases.   On November the 21st, the temperature was submormal, and collapse was very evident.   The pulse was noted to be very irregular and rapid although polygraphic tracings were not obtained.   The next day the child died.

Polygraphic curves of CASE 3.

On November the 17th, the eighth day of illness, polygraphic curves represented by Fig. 14 were obtained.   The venous curves in this figure seem to be open to two interpretations.   It is obvious that there is no wave during the ventricular diastole representative of separate and co-ordinate contraction of the auricle.   It would seem, therefore, that we are dealing either with a nodal rhythm or auricular fibrillation with heart block.   With the first interpretation the ventricle *c* contracts before the auricle as figured in the second and third cycles.   With the second interpretation the second broad wave is a *v* wave only.
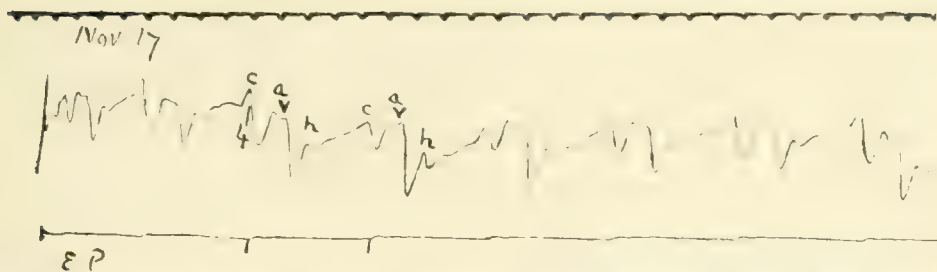
Fig. 14. Jugular and radial curves from *CASE* 3. After the diastolic period of each cycle a *c* wave indicates the beginning of ventricular systole. This is followed by a broad wave which is thought to include *a* and *v* components. *h* = the wave of Hirschfelder and Gibson.
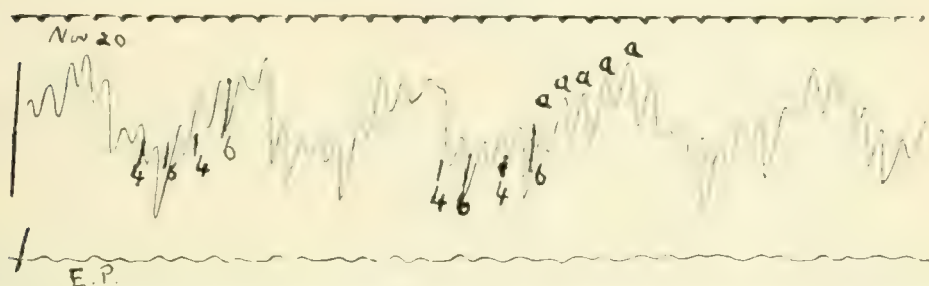
Fig. 15. Jugular and radial curves from *CASE* 3. The venous curve is deformed by respiratory movement. Regular waves due to auricular contraction are marked *a*. The line 6 falls between two waves.
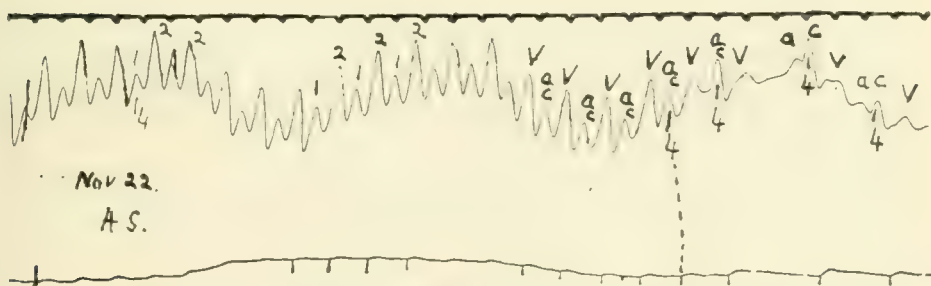
Fig. 16. Jugular and radial curves from *CASE* 4. They show the termination of the paroxysm; during the paroxysm the jugular curve is composed of two waves in each cardiac cycle (marked 1 and 2), also *ac* and *v*. The radial curve is small and uneven as the hand was moved, and the commencement of the radial upstroke is indicated.

Similar curves were obtained on November the 18th and 19th and were succeeded on November the 20th by the curves represented in Fig. 15. In this figure small waves appear throughout the venous curves and it is impossible to assign their causation to the factors which produce a normal rhythm. For instance, the marking 6 which usually corresponds to the apex

and commencement of the downstroke of a wave in the jugular curve is found to be midway between two waves in this instance. It is thought that each of the regular waves in the jugular tracing is indicative of a co-ordinate contraction of the auricle.

Post-mortem examination of CASE 3.

The post-mortem examination was made on the day of death. The pleural and pericardial cavities were clean ; though the lungs were congested, there was no evidence of the broncho-pneumonic patches which were present in the first two cases. The heart had the same naked eye appearances as have been described in *CASES* 1 and 2. The right auricular appendix was wholly occupied by an adherent ante-mortem clot. All the cavities of the heart were dilated but the valves were healthy. The heart muscle was pale, soft and friable. The kidneys had the appearance of intense cloudy swelling and the liver was fatty. As in the previous cases the following regions of the heart were submitted to microscopic examination, and their appearances are now described.

The sino-auriculo node. The node was large and well defined. The nodal tissue was infiltrated by large numbers of mononuclear cells of the formative type. The capillaries were engorged and in places actual hæmorrhages had occurred. The muscle fibres were in a condition of granular degeneration.

The auriculo-ventricular node and bundle was found in 130 sections of 12 micra thickness. The node was well formed and beyond some slight vascular engorgement was quite normal. The bundle also was well formed and was traced into right and left branches. Throughout its course the fibres were perfectly normal and there was no vascular engorgement.

The auricular muscle showed a slight degree of fatty degeneration similar to that described in *CASES* 1 and 2. *The ventricular muscle* was the seat of an intense fatty degeneration, though there was no interstitial myocarditis.

CASE 4.

Clinical history of CASE 4.

Child aged 6 years, was admitted on October the 15th, 1912. She had been ill for two days and her illness had begun with sickness, vomiting and dysphagia. On admission both tonsils were covered by membrane and the right submaxillary gland was enlarged. Albumen was present in the urine. The temperature was 99·6° and the pulse rate 144. Beyond the rapidity no other cardiac abnormality was detected. 4,000 units of antitoxin were administered.

On the next day the throat was cleaner but it was thought advisable to inject 4,000 units of antitoxin. The first sound of the heart was short and sharp, and its character was that of a second sound. Up to the sixteenth day of illness, October the 28th, the rhythm of the heart was quite regular and beyond some outward displacement of the apex and weakening of the first sound, no other cardiac abnormality was discovered. On October the 28th, however, the regularity of the heart was frequently interrupted by premature beats.

On November the 1st, nasal phonation was noticed and milk was regurgitated through the nose. The temperature was 98·2° and the pulse rate 88. At this time the child was listless and pale, and the extremities were cold. During the next three weeks she seemed to improve and beyond marked prostration there was nothing worthy of note, though the first sound of the heart was feeble and the apex was in the nipple line. On November the 22nd, the forty-first day of illness, the child vomited frequently and became very collapsed. Polygraphic records taken on this day showed that the attack was associated with both short and long periods of paroxysmal tachycardia which recurred at intervals.

On December the 2nd, the fifty-first day of illness, the events of November the 22nd were repeated. On both occasions the child was very ill and it seemed impossible that she would recover on either occasion. But she was discharged cured on February the 21st, 1913, having been in the hospital for four months.

Polygraphic curves of CASE 4.

Paroxysmal tachycardia. Only one paroxysm of tachycardia has been recorded in this series of cases and it occurred in the present instance (*CASE* 4). Although the origin of the abnormal rhythm may have had its seat in the auricular musculature, I think it probable that the auriculo-ventricular node was the generating focus. The attack, the termination of which is represented in Fig. 16, lasted for twenty-five minutes and was accompanied by the signs and symptoms of cardiac distress which are associated with paroxysmal attacks of tachycardia. The tracing represented in Fig. 16 was taken on the forty-first day of illness, and similar attacks were frequent on that day. The analysis and interpretation of this tracing must be discussed as the paroxysm may have originated in the auricular muscle or in the *A- V* junctional tissues (node of Tawara and bundle of His). Each cardiac cycle is represented by two waves in the venous curve, a small wave (marked 1) and a larger wave (marked 2). The time of the radial upstroke (marked 4) is found to follow the upstroke of the smaller wave by less than one-tenth of a second. If the paroxysm was generated in the auricular musculature, the wave *a* due to auricular systole must either be included in the small wave of its own cycle or in the larger wave of the preceding cycle. A consideration of the *a-c* interval militates against the acceptance of either of these interpretations. Firstly, on the assumption that the upstroke of the small wave indicates the beginning of auricular systole, the *a-c* interval is excessively short, much less than one-tenth of a second. Secondly, if the *a* wave lies in the large wave of the previous cycle the *a-c* interval is abnormally long when the rapid rate of the heart beat is considered. Also, the last cycle of the paroxysm is delayed, and with this interpretation a sudden lengthening of the *a-c* interval has to be assumed. This would be very unusual. That the paroxysm has its origin in the *a-c* nodal tissues seems more probable. If this is the correct interpretation the small wave is composed of auricular and ventricular elements (*a* and *c* waves) and the larger wave is a *v* wave, whose apex coincides with the bottom of the dicrotic notch of the radial curve. The paroxysm ends abruptly and a typical post-paroxysmal pause occurs before the normal rhythm is re-established. By polygraphic and electrocardiographic methods Lewis[8] has shown that attacks of paroxysmal tachycardia may arise in the nodal

tissues, and under nodal rhythm it has been shown that there is a tendency in the diphtheritic heart for the A-V node to become the originator of the cardiac rhythm. As far as I am aware no instance of paroxysmal tachycardia has been recorded in diphtheria. In the patient from whom this tracing was obtained other similar attacks occurred on December the 2nd, after which convalescence began and no other heart irregularity was detected.

DISCUSSION.

It is interesting to note the similarity—both clinical and pathological—which existed in the first three cases. All three children attended the same school and presumably contracted the disease from the same source. The duration of the illness which terminated fatally in all three cases was almost identical, as two of them died on the thirteenth day of illness and the third died on the fifteenth day of illness. The march of the disease from day to day gave rise to changes in the clinical picture which followed each other with such regularity that one description might have served for all three cases. The vomiting, pallor, gradual dilatation of the heart, the altered character of the heart sounds, the types of arrhythmia, the subnormal temperature and the other manifestations of toxæmia were present in almost each particular in all three cases. This coincidence is particularly striking in the time of appearance of the various types of arrhythmia. Premature beats of the heart, which were proved to be of auricular origin in one case and probably also were so in the other two cases, appeared on the ninth day in two cases and in the third case on the seventh day. In two cases a nodal rhythm appeared on the tenth day and in the third case on the eighth day. A condition thought to be auricular flutter was noted in two of them; in one instance on the eleventh day and in the other on the twelfth day.

The fourth case stands apart, and is of a different type; in this case the heart weakness was heralded by auricular extrasystoles and was prolonged, and the patient was subject to paroxysms of tachycardia.

And now brief reference may be made to each variety of irregularity.

Auricular extrasystoles. In all four cases premature cardiac beats were detected by examination of the heart and of the radial pulse and were the first signal of the later and more marked irregularities. The premature beat has been shown to be of auricular origin in *CASE* 1, and in two other cases apart from this series I have obtained tracings which prove the auricular origin of similar premature contractions. The frequency and the time of appearance of premature beats in cases of diphtheria are at present the subject of investigation, and will form the basis of a further communication on the heart irregularities in this disease.

Nodal rhythm. Under this title an attempt has been made to prove that the auricles and ventricles contract as the result of a stimulus from a

common focus and that such a common focus resides in the auriculo-ventricular junctional tissues. As this rhythm is unusual in the human heart it is necessary to review the support which can be found for this conclusion on experimental and clinical grounds. Experimentally, a nodal rhythm is said to have been produced under three different conditions :—

1. Engelmann[5] tied a Stannius' ligature between the sinus venosus and the auricles of a frog's heart, so that no portion of the sinus structure was left on the auricular side of the ligature. The auricles and ventricles contracted independently of the sinus venosus ; the response was such that either the auricle and ventricle contracted together or the ventricular contraction preceded the auricular contraction.

2. Cushny[1] injected aconitine into the circulation of dogs and produced a reversal of the normal heart beat, the ventricle contracting before the auricle. By repeated electric stimulation of the ventricles and the application of iced saline, he was able to cause simultaneous contraction of both auricles and ventricles. Cushny also states that " simultaneous contraction of the auricles and ventricles may be obtained by passing a shock through the auricle and ventricle by electrodes, one of which is placed on the auricle and the other on the ventricle."

3. Rothberger and Winterberg[12] produced a simultaneous contraction of auricles and ventricles in animals by stimulation of the left sympathetic nerve. A nodal rhythm was obtained in 30% of their experiments, and the ventricle frequently contracted before the auricles.

Though I am not aware that others have recorded a clinical type of nodal rhythm identical with those which are now recorded, there are certain instances in previous reports which bear a marked similarity to this form of arrhythmia. Mackenzie[9] suggested that premature beats might arise in the *A-V* node (nodal extrasystoles) and published tracings in which extrasystoles disturb a normal rhythm, where both the auricular and ventricular components of the extrasystole were premature. More recently Cowan, Fleming and Kennedy[2] have published three cases in which the rhythm of the heart was regular, but the *a-c* interval was so short (·06, ·10, ·10) that they were unable to believe that the rhythm was generated in the normal pacemaker (*S-A* node) and assumed a common site of origin in the *A-V* tissues. Post-mortem in these cases the *A-V* node was found to be the seat of an acute inflammatory process. A similar rhythm was thought to exist in a case published by Cowan and Ritchie[3] in which the *a-c* interval measured at ·10 second. Belski[1] also shows tracings which seem to demonstrate simultaneous contraction of auricles and ventricles in cases of acute rheumatism, typhoid fever and scarlatina. Hecht[7] has published polygraphic and electrocardiographic tracings obtained from a child of 7 years suffering from pharyngeal diphtheria, which are thought to indicate a nodal rhythm.

The suggestion that the true pacemaker of the heart (the *S-A* node) is in abeyance and that its function is usurped by the auriculo-ventricular node seems to meet with some pathological support. Because the most acute inflammatory lesions were discovered in the region of the sino-auricular node while the auriculo-ventricular node was unaffected.

Heart-block. Magnus-Alsleben,[10] T. B. Fleming and A. M. Kennedy,[6] Price and Ivy Mackenzie,[11] have published instances of heart-block in diphtheria, and it is noteworthy that the authors of the last case found that the main stem and branches of the auriculo-ventricular bundle were normal. In my own case the bundle was the seat of some capillary engorgement which was not present in the other two cases.

Auricular flutter. That the jugular curves contained in Fig. 9 and 15 in *CASES* 1 and 3 respectively are indicative of auricular flutter is a tentative interpretation. It is recognised that the speed of the auricles, which this view assumes, is very great, varying as it does between 480 and 500. In no case of auricular flutter hitherto published has the auricular rate exceeded 350 beats per minute, though all such instances were in adults. It may be possible that the auricles of the child can attain a higher speed.

In conclusion, it is believed that the systematic examination of the heart in severe cases of diphtheria by graphic methods will corroborate the discovery that many forms of arrhythmia occur in this disease which cannot be recognised by ordinary methods of examination.

I have great pleasure in acknowledging the debt which I owe to Dr. S. J. Clegg, the Resident Medical Officer, City Hospital for Infectious Diseases, Newcastle-on-Tyne, for his interest in the subject and the valuable assistance which he afforded me in the investigation of the cases.

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OBSERVATIONS RELATING TO DYSPNŒA IN CARDIAC AND RENAL PATIENTS.

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THE observations of the present paper were suggested by certain general observations upon breathlessness in patients who are the subjects of heart disease. They were suggested especially by a comparison of the degree of breathlessness and the degree of cyanosis in certain groups of cases. There are forms of congenital disease of the heart where the venous blood passes into the systemic arteries through openings which short-circuit the lungs, and where much of the blood is transferred from venous to arterial system in an unaerated condition; in these subjects, blueness is a conspicuous manifestation. Yet it is a noteworthy fact that in many of these patients, as they lie in bed, dyspnœa may not be great. It appears from this observation that deficient aeration of the blood as it enters the aorta, thence to be distributed, has to be considerable before urgent dyspnœa is exhibited. Now although a proportion of those heart patients who suffer from laboured breathing show what may be termed deep cyanosis, yet a large, if not equal, number, though breathless, are far less blue. In extreme instances the breathlessness of a patient may be urgent, yet cyanosis may be slight or even absent. It becomes apparent that lack of aeration is an insufficient explanation of breathlessness in a large proportion, if not in the majority of very breathless patients. It matters not if the breathlessness be attributed to slow circulation through the lungs or to obstructed air entry, the same argument applies; a patient who suffers from deficient blood aeration must inevitably be blue, and if he be very breathless as a result, blueness must be conspicuous. In renal disease, in many patients who are said to suffer from emphysema and bronchitis and, lastly, in many cases of heart disease, this association of breathlessness with an equivalent degree of cyanosis is not witnessed. In all such patients some cause of breathlessness, apart from the purely physical relations of blood and air in the alveoli, has to be found.

We commenced our study by investigating such subjects of heart disease who, while extremely breathless, showed but slight grades of cyanosis, and arriving, as we think, at a satisfactory explanation of the dyspnœa in these patients have extended our search. We have included cases in which cyanosis was distinct or moderately deep, but in which at the same time it has been felt that, considered as an index of deficient aeration, the cyanosis accounted imperfectly for the degree of accompanying dyspnœa. In these cases also an additional cause of breathlessness has been found. The cause in the first group, and the additional cause in the last, is the same, namely, relative acidity of the blood ; an acidity which is not due to an excess of carbonic acid gas. The observations as a whole give to breathlessness, especially as it is observed in cardiac patients, a new aspect, and suggest the possibility of eventually linking together types of dyspnœa hitherto considered distinct.

There are more particularly two classes of patient who exhibit breathlessness, as yet of unexplained origin. In one class the predominating lesions are renal, and to breathlessness, occurring in such subjects, the term "uræmic dyspnœa" is usually applied ; on the other hand, there is a class in which the heart appears to be the chief seat of mischief, and the breathlessness is often sudden in its onset, or periodic in its intensity, increasing in severity it may be at night, and meriting according to many writers the term "cardiac asthma." Our investigations include cases which would be placed in the uræmic group by some, and cases which would be placed in the "cardiac asthmatic" group by others. Whether a given case belongs to one group or to the other, is oftentimes a matter of opinion or terminology. The terms "uræmic dyspnœa" and "cardiac asthma" are differently employed by different observers ; inevitable confusion follows ignorance of the underlying cause of the chief symptom. While the present investigation suggests the identity of "cardiac asthma" on the one hand and "renal asthma" on the other, an extension of the observations should finally and definitely separate them or link them together.

We may waive further discussion of this subject for the present, and with more profit may describe briefly the clinical associations of a certain form of acid intoxication, as they are at present positively known to us ; leaving future observations to add other types in which the breathlessness proceeds from a similar cause.

CLINICAL ASSOCIATIONS OF THE ACIDOSIS.

The most striking feature of the acidosis which we shall describe is breathlessness, and breathlessness in a subject who is neither conspicuously anæmic, nor conspicuously cyanosed. The patients of our series, in which this symptom has occurred, have been elderly ; the youngest subject being 50 years of age. The onset of the dyspnœa may be sudden (as in *CASE* 12), though more usually it is gradual. It fluctuates in degree, so that at one time the patient may breathe freely, while at another time the struggle for

breath may be extreme ; more customarily, there is constantly some breathlessness, but periodically it increases. An increase with exercise is almost always spoken of ; an increase in the recumbent posture is witnessed to by the almost invariable orthopnœa. Yet orthopnœa is not a necessary accompaniment (CASE 4). An intensification at night of unexplained origin* is extremely frequent ; the patient often awakens to feel himself suffocating and the struggle for breath, often of a most distressing kind, may be maintained for a few minutes, a half hour or longer. Periodic breathing of the Cheyne-Stokes type is present in a large proportion of the patients ; but this symptom may lack conspicuousness ; there may be no real apnœa but a simple waxing and waning of the tidal flow or a waxing and waning of the residual capacity. The sign may require very deliberate search to elicit it ; otherwise it frequently escapes notice. For this reason, curves of respiration have been taken in all our cases, and usually on many occasions in each case.

Wasting is frequent and often considerable ; anæmia is present in some degree in most instances, but is usually slight in extent. Drowsiness and general apathy are often present, and may finally deepen to coma.

The heart shows enlargement in all cases, the chambers are dilated and hypertrophied ; gallop rhythm is frequent, murmurs are infrequent, though any valve lesion may be present. The heart's mechanism may be normal, and when this is the case the pulse frequency is raised, lying usually between 80 and 100 and being more frequent towards evening. Many different perversions of mechanism have been seen ; they may take the form of extrasystoles, paroxysmal tachycardia, auricular fibrillation, heart-block or alternation. Angina pectoris may be present. The heart muscle may be fatty ; coronary disease is the rule. Dropsy, when present, has always been of the cardiac type. Venous stasis is usual, though its amount varies ; the veins are generally full, and the liver enlarged. The degree of cyanosis and the degree of orthopnœa usually goes hand in hand with the other signs of stasis. A general atheromatous condition of the vessels is the rule ; the blood pressure is often very high, but may be normal.

When there are few signs of venous stasis, the urine is increased in quantity ; the presence of albumen and granular casts is customary. Dryness of the mouth and thirst are often experienced by the patients. Retinitis has not been seen ; vomiting and cerebral attacks, in the form of convulsions or hemiplegia have been encountered on more than one occasion. Headache may be severe. A retention of urea was found in three cases, all of which died within twenty-four hours (CASES 1, 2 and 3) ; in one of these cases the retention developed while the case was under observation. The

* These attacks are not the result of apnœic periods in the breathing ; they are found in patients in whom Cheyne-Stokes breathing is not seen (CASES 9 and 10) ; and in those in whom this symptom occurs, the distress is an accompaniment of rapid breathing (CASE 5) ; drowsiness and apathy mark the apnœic stage, of which the patient is unconscious. Later it will appear that the condition of the blood is very similar to that which obtains at high altitudes. The acute symptoms of mountain sickness often come on at night.

kidneys may be of the red granular generally contracted type (*CASE* 3), or of the arterio-sclerotic type (*CASES* 8 and 11) ; more frequently they are enlarged and show a fine granular surface and on section considerable arterial disease and fibrosis. In no instance have normal kidneys been found.

A subnormal temperature is the rule. The condition usually ends fatally within a short time, and especially is this the case where signs of cardiac failure are prominent.

In the succeeding account we shall refer to these patients as the *special* cases, to distinguish them from the cases of simple cardiac dyspnœa which were also examined.

BLOOD GAS ANALYSES.

We decided to examine, in the first instance, the blood gases of the " special cases " which have just been described, in the hope of discovering a chemical stimulus, the presence of which might be regarded as activating the respiratory centre. We examined at the same time, and for comparison, cases of simple cardiac dyspnœa. In both groups a chemical stimulus was found, but the stimulus is not identical in the two groups, as will be seen in the succeeding section of this paper.

Testing for a chemical (acid) stimulus.

The method is based upon the view* that the respiratory centre is stimulated by acid. The simplest and no doubt the commonest acid is CO_2 but other acids produce the same effect. For example, in exercise the respiration quickens because of the production of carbonic acid which increases the concentration of that gas in the blood and so stimulates the respiratory centre, the evidence of increased concentration of CO_2 in the blood is the increased presence of CO_2 in the alveolar air of the lung.

But this simple mechanism, which involves only the blood, the brain and the lung, is one which becomes rapidly superseded during exercise by a more complicated one ; not only is carbonic acid produced, but also lactic acid. These jointly stimulate the respiratory centre. Yet, in order to get the blood back to its normal condition, both the lungs and the kidneys are involved ; but whereas CO_2 is rapidly got rid of by the lungs, lactic acid is slowly got rid of by the kidneys. Inasmuch, therefore, as the duration of the stimulus to the respiratory centre lasts till the blood gets back to its former reaction (the nature of the acid being indifferent), the general result of long exercise is to increase the lactic acid in the blood at the expense of the carbonic acid, there is, in fact, an obvious lactic acidosis. The following changes may therefore be discerned in the blood by appropriate methods during continued exercise.

1. The balance of acids, including carbonic acid united to bases in the blood, changes, shifting in the direction of greater acidity.

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* Although the bald statement we have made is to some extent controversial we have not considered it necessary to go into the historical evidence on which this view is based ; this will be found in any modern text book, *e.g.*, those of Starling or Zuntz and Lowy, second edition.

2. There is considerable lactic acidosis which can only be set right by the kidney.

3. There is a fall in the concentration of CO_2 in the blood, as testified by the fall of CO_2 pressure in the alveolar air.

These facts with regard to the reaction of the blood may best be observed by using the affinity of oxygen for hæmoglobin as an "indicator." Any shifting of the reaction of the blood in the acid direction means a decreased affinity of the corpuscles for oxygen ; any shifting in the alkaline direction means an increased affinity for oxygen.

Fig. 1 shows the effect of increasing amounts of CO_2 on the affinity of human blood for oxygen. Plotted horizontally is the oxygen pressure, and
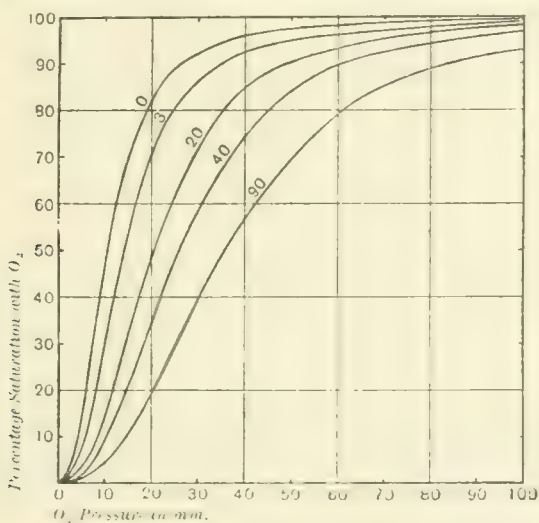
Fig. 1.

vertically is the quantity of oxygen united with the blood. Inasmuch as different samples of blood have different hæmoglobin values, it would be erroneous to plot the absolute amount of oxygen united with the hæmoglobin as the ordinate, but rather the percentage of oxygen relative to the whole oxygen capacity of the blood.

Of these curves that determined in the presence of 40 mm. pressure of carbonic acid is the actual dissociation curve of the blood of the person as it exists in his body normally. The person from whom this blood came then has a normal alveolar pressure of 40 mm. of CO_2 ; to test whether his blood has its normal properties, a small quantity, say about 1·3 cc., is put in a tonometer (Fig. 2) of about 250 cc. capacity. The tonometer has previously been filled with nitrogen, oxygen (say 30 mm.) and CO_2 (40 mm.). The tonometer is rotated in a bath at the temperature of the body, and when equilibrium has been attained, the blood is withdrawn and its percentage saturation with oxygen measured by the differential method.* The gas in the tonometer

* Barcroft and Roberts. *Journ. of Physiol.,* 1910, *xxxix*, 429.

is also analysed. In the case stated. *i.e.*. where the CO_2 pressure is 40 mm. and the oxygen pressure is 30 mm. the percentage saturation of the blood should be 58%. If it is less than this. the reaction of the blood has shifted in the acid direction ; if more than this. the reaction has shifted in the alkaline direction.
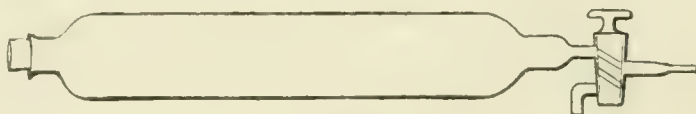
Fig. 2.

The condition in which the blood takes up less than its usual share of oxygen is called *meionexy* ; the opposite condition, that in which it takes up more than its usual share, is called *pleonexy*. Meionexy indicates a shifting of the reaction in the acid direction. If the blood were meionectic, we should expect stimulation of the respiratory centre.

It is desirable to be able to express the degree of meionexy in units. For this purpose, advantage can be taken of the fact that these curves do not appear to be fortuitous. but are capable of expression by a general formula.

This formula* is based on the conception that the inter-action between hæmoglobin and oxygen is a reversible chemical change ; the molecules of oxy-hæmoglobin form at a certain velocity from oxygen and reduced hæmoglobin and again break up at another velocity into oxygen and hæmoglobin ; the ratio of these velocities, the one to the other, is signified by the letter K. The molecules of hæmoglobin are not single molecules, but are aggregated together in groups. the average number of molecules in each group is signified by the letter n. If now the oxygen pressure is x, and the percentage saturation y :

$$\frac{y}{100} = \frac{Kx^n}{1 + Kx^n}$$

Inasmuch as a change in reaction does not appear to influence n to any appreciable extent. the equation practically only contains one variable, namely K. and the curve in which a given point lies is established if the value of K is known.

The values of K for the curves given above are :—

0 mm. CO_2	·00258
3 mm. CO_2	·00130
20 mm. CO_2	·000505
40 mm. CO_2	·000292
90 mm. CO_2	·000135

* Hill (*Proc. Physiol. Soc., Journ. of Physiol.*, 1910, *xl. v*). Douglas Haldane and Haldane have suggested a much more complicated formula which might equally have been used. Our reasons for regarding the simpler one as the more accurate are set forth in a paper by Barcroft and Hill at present in the press in the Biochemical Journal

Therefore, as the reaction shifts in the acid direction, the value of K falls, or the more meionectic the blood, the smaller the value of K.

Now K has not quite the same value even in normal persons; taking men of various ages and modes of life, it varies within limits of approximately ·00036 — ·00021. It seemed desirable to ascertain within what limits K stood in the case of hospital patients, whose ailments were such as not to involve the probability of any change in reaction of the blood. These show a greater degree of constancy, probably because they live more uniform lives, and are more of an age than the generality of mankind.

The following control cases were determined.

Determinations in simple controls.

CASE.	SEX	AGE	AILMENT.	K.
16. H. H.	Male	45	Gastric	·00027
17. R. G.	Male	58	Appendix (convalescent)	·00028
18. W. S.	Male	61	Rectal fistula (convalescent)	·00025

As controls we also used the "special cases" after they had recovered from their dyspnœa, temporarily, at all events.

Determination in special controls.

CASE.	SEX	AGE		K.
1. J. P.	Male	69	(2nd observation)	·00023
9. M. P.	Female	61	(2nd observation)	·000274
12. R. J.	Male	56		·00033

Taking these cases together, the limits in the value of K are ·00023 — ·00033. A more accurate idea of what these figures mean may be derived from Fig. 3. The black area may be regarded as that within which any curve may be expected to fall, if the reaction of the blood is to be regarded as normal.

In comparison with the controls and special controls, which have a value for K between ·00023 and ·00033, stand the cases of dyspnœa. All the dyspnœic cases had values below ·00022.* The following values of K were found for dyspnœic cases; they are grouped into special cases of dyspnœa and cases of simple cardiac dyspnœa.

*With the exception of CASE 15. This patient showed a little dyspnœa, but K was estimated at ·00034. We could find no evidence of an acid stimulus, CO_2 or otherwise, in his blood. It is probable that the alveolar CO_2 was considerably underestimated, or that a reflex factor was present in this case. We have consequently excluded him from our tables.

Special cases of dyspnœa.

Case.		Sex.	Age.	Date of Observation.	Value of K.
1.	J. P.	Male	69	7.3.12	·00018
				7.4.13	00008
					·00011
2.	H. L.	Female	66	5.5.13	·00013
				23.5.13	·00019
3.	G. S.	Male	67	29.4.13	·00013
4.	D.	Male	57	8.5.13	·00022
5.	F. C.	Male	53	29.1.13	·00012
					·00015
				5.2.13	·00010
					·00016
6.	A. S.	Male	57	19.5.13	·00021
7.	F. S.	Male	63	14.5.13	·00020
				21.5.13	·00020
9.	M. P.	Female	61	23.5.13	·00020
10.	H. P.	Male	50	28.4.13	·00016
		Simple	*cardiac*	*dyspnœa*	
13.	T. C.	Male	49	21.4.13	·00020
14.	E. M.	Female	29	4.6.13	·00021
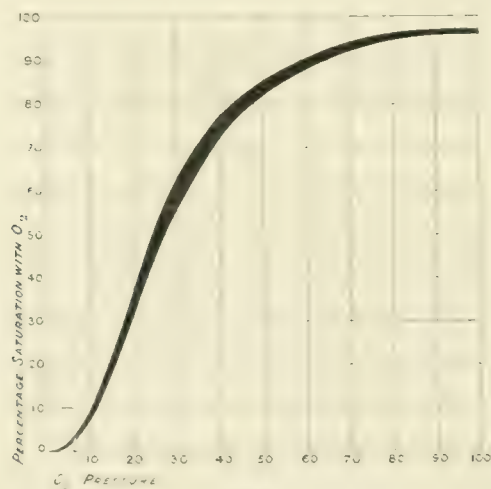
Fig 3

This. then, is the first point ; the dyspnœic cases had abnormally low values for K ; and were therefore meionectic. In the " special cases " as in the simple cardiac cases, the dyspnœa was shown to be due to a chemical stimulus, namely increased acidity of the blood.

When first we discovered that some of these cases appeared to be meionectic, a possible fallacy occurred to us.

Morawitz has pointed out that under certain circumstances, blood will reduce itself to an appreciable extent in a short time. It seemed possible that this might be taking place in our apparatus, and that during the process of analysis the blood might be undergoing self reduction, an event which would, of course, give abnormally low percentage saturation. The circumstance under which Morawitz observed this phenomenon was anæmia, either in pathological conditions, or as the result of the withdrawal of considerable quantities of blood from the circulation. He attributed it to the metabolism of a large number of freshly formed red corpuscles in the circulation. Although in the subjects of the present research anæmia was, at most, slight, it seemed desirable to investigate the question of whether the blood possessed any exalted power of reducing itself. This test was carried out in two ways. (1) At 107 mm. oxygen pressure both normal blood and blood which is meionectic to the extent observed in these investigations are practically fully saturated with oxygen, 98%, or over. This pressure is attained by putting atmospheric air in the tonometer and then heating up to 37 C. Suppose now we take three tonometers, A, B and C.

Into A put air, CO_2 (40 mm.) and blood from a normal person.
Into B put air, CO_2 (40 mm.) and blood from the patient.
Into C put oxygen 30 mm., CO_2 40 mm. and blood from the patient.

If there is no self reduction of the blood during analysis, the difference between the percentage saturation of A and C and of B and C will be, to all intents and purposes, the same; but if the blood of the patient reduces itself, both B and C will give readings which are too low, and therefore the difference between A and C will be greater than between B and C. This test was performed in the blood of a patient (CASE 5), with the result that there was found to be no appreciable self reduction. (2) In the case of another patient (CASE 1), a small quantity of blood was shaken with air and drawn into a glass syringe, the orifice of this syringe was closed with a cap of plasticine and the whole incubated for 45 minutes at 37°. At the end, no reduction was found to have taken place.

In the light of these tests, our deduction that the dyspnœic patients were meionectic remained valid.

Alveolar air analyses.

It is essential to the above test for the reaction of the blood that the patients' blood should be exposed in the tonometer to the carbonic acid pressure of his alveolar air whilst the test is being carried out. It is, therefore, necessary to determine the composition of the alveolar air in each case. This was done by the method of Haldane and Priestley.[11] The alveolar air was received into a vacuous tube, and was subsequently analysed by Haldane's method. Two or three samples were usually taken: the results given by those taken from most of the members of our series differed more than those from a person accustomed to serve as the subject for such determinations. Moreover, in some cases, the movements of the chest were so restricted as to make the determinations very rough ones. Nevertheless, it is clear that there is a wide departure in many cases from the normal value which may be considered as 36-42 mm..

The following is the alveolar air determination from the cases cited above, which we regard as control cases:

Simple controls.

Case.	Alveolar pressure of CO_2 in mm.
16. H. H. ...	40, 38, 38
17. R. G.	35·5, 36·8
18. W. S. ...	41, 41, 39

Special controls.

Case.	Alveolar pressure of CO_2 in mm.
1. J. P. (2nd obs.)	25, 31
9. M. P. (2nd obs.)	40, 41
12. R. J.	Doubtful

Taking these therefore as normal figures of patients whose respiration was unaffected, the following figures from the dyspnœic patients should be compared with them.

<center>*Special form of dyspnœa.*</center>

CASE.		Alv. CO_2 in mm.	DATE.
1.	J. P.	34, 30	7.3.13
		26	7.4.13
2.	H. L.	31	5.5.13
		29	23.5.13
3.	G. S.	13	
4.	D. ..	27, 30	
5.	F. C.	28, 27	29.1.13
		25, 27, 28	5.2.13
		31, 27, 31	14.2.13
6.	A. S.	29, 26	
7.	F. S.	34, 34, 31	14.5.13
		32, 41, 33	21.5.13
9.	M. P. (2nd obs.)	36, 33	
10.	H. P.	27	

<center>*Simple cardiac dyspnœa.*</center>

13.	T. C.	46, 47	
14.	E. M.	39, 43, 41	

When first we found these low CO_2 values in the " special cases " it seemed possible that they might be due to some unobserved error in the apparatus. With exactly the same apparatus, control tests were done on one of us, which gave the normal alveolar pressure of 40 mm. and respiratory quotient of ·9 (see the consideration of respiratory quotients later).*

The most obvious feature of the above data is the relative absence of figures ranging between 35 and 40 mm.. The cases range themselves into two quite distinct groups ; those on the high side of the control cases and those which range considerably below the control cases. Whilst it is possible that there may be sufficient excess of carbonic acid in the blood of the simple cardiac dyspnœas (*CASES* 13 and 14)† to explain the rather moderate degree of meionexy observed in these cases, it is clear that the remaining cases of meionexy cannot be explained in this way, for in all of them the alveolar CO_2 pressure, so far from being increased, was diminished ; in some cases diminished to a remarkable degree. It was necessary to seek another cause for the meionexy in the form of excess of non-volatile acids in the blood.

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* Straub and Schlayer[1] found low tensions of alveolar CO_2 in a number of uræmic patients, and have suggested acidosis as the cause.

† The normal alveolar CO_2 pressure in women is somewhat lower than in men.

The test for acidosis (non-volatile).

Excluding the change in reaction due to alteration in the carbonic acid, is there evidence of the accumulation of other acids in the blood in the cases to which reference has been made ? Take, for instance, the blood of *CASE 5*; is there evidence of its being more acid than that of *CASES* 16 and 17 ? This question we set ourselves to answer. Here again, we used the affinity for oxygen as an " indicator."

The following curves (Fig. 4) are those of the blood of one of us (J. B.) mixed with various quantities of lactic acid added.* There is no question
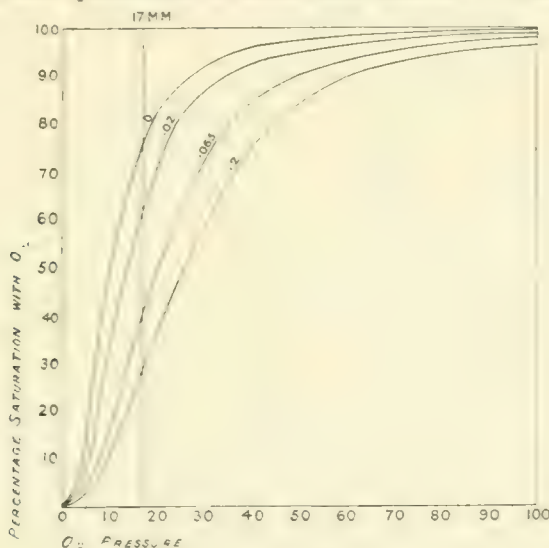
Fig. 4

of CO₂ in this series : it was shaken out of the blood before the experiment was commenced. And the gas in the tonometer was free from it, or at least contained less than 1 mm..

Over a portion of the figure, the difference in the percentage saturation caused by the addition of successive increments of lactic acid is very great. As a standard, an oxygen pressure of 17 mm. has been used, the same as that used by Mathison, in whose hands the test was first operated.

It will be clear from the figures that this property might be used for the estimation of lactic acid in blood for since at 17 mm. oxygen pressure :

Normal blood   is 75% saturated.
,,   ·02%,, lactic acid is 60%,,   ,,
,,   ·04%,, lactic acid is 49 %,   ,,
,,   + ·08%, lactic acid is 34%   ,,

A curve may be drawn relating the quantity of lactic acid added to the percentage saturation of the blood at 17 mm. oxygen pressure. Armed with this curve, it is only necessary to expose a sample of blood containing lactic acid to 17 mm. oxygen pressure and determine the percentage saturation with oxygen, in order to find out the quantity of lactic acid added.

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* That with 2%, lactic acid is only an approximation.

And since what is true of lactic is true of other acids, we can express any change in reaction of the blood in terms of the quantity of lactic acid which would have to be added to normal blood in order to give the percentage saturation observed when the blood is exposed to 17 mm. oxygen pressure.

The experimental manipulations are precisely of the same type as those already described for the test for meionexy, except that the CO_2 is omitted.
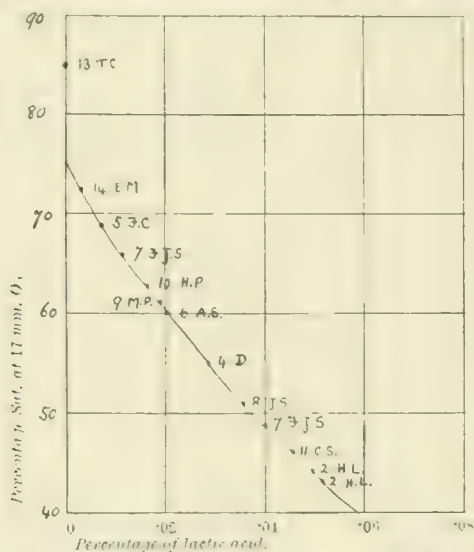
Fig. 5.   A diagram of the relative degree of acidosis (non volatile), expressed as lactic acid, and calculated from the percentage saturation of hæmoglobin exposed to 17 mm. O_2 pressure, in the dyspnœic cases.

It has been stated above, that normal blood is 75% saturated with oxygen when in equilibrium with an atmosphere of 17 mm. oxygen pressure at $37°$ C. This statement requires some modification, for here again there are slight differences in different persons. Mathison, testing five cases, got variations of from $66\text{-}79\%$. Boothby and Barcroft, working under more advantageous conditions, especially as regards the absence of CO_2, obtained a figure between 69 and 79%.

In the present series of experiments, we have performed the test upon the control patients, to whom allusion has already been made, as well as on some others, with the following results.

Percentage saturation of blood with oxygen at 17 mm. pressure and at $37°$ C..   *Control cases (no dyspnœa).*

CASE.		Percentage saturation of oxygen at 17 mm. O_2 pressure in absence of CO_2.
16.	H. H... ..	69. 75%
17.	R. G.	80%
18.	W. S. ..	75%

Special control cases (no dyspnœa but little reserve).

CASE.		Percentage saturation of oxygen at 17 mm. O_2 pressure in absence of CO_2.
1.	J. P. (2nd obs.)	59.5%
9.	M. P. (2nd obs.)	74%
12.	R. J. ..	60%

With the exception of cases which had been dyspnœic (and which still lacked full reserve), the controls range themselves roughly between 70 and 80% saturation.

With these should be compared the two classes of dyspnœic case to which we have alluded.

" Special cases " of dyspnœa, in which there is a low alveolar CO_2 tension.

Case.	Alv. CO_2 (mean).	Percentage saturation at 17 mm. O_2 in absence of CO_2.	Equivalent of lactic acid necessary to produce change in reaction.
1. J. P. ..	26	14%	·15%
2. H. L. ..	31	44%	·05%
4. D.	29	43%	·05%
	27, 30	55%	·03%
3. G. S. ..	13	14%	·15%
5. F. C. ..	28	69%	·007%
6. A. S. ..	27	60%	·02%
7. F. S. ..	33	48%	·04%
	36	66%	·015%
8. J. S. ..		50, 52%	·035%
9. M. P (1st obs.)	34	61%	·02%
10. H. P. ..	27	62, 63%	·017%
11. C. S. ..		46%	·045%

Simple cardiac dyspœna, in which there is a high alveolar CO_2

13. T. C. ..	47	84, 86%	nil.
14. E. M. ..	41	71%	nil.

The " special cases " differ from those of simple cardiac dyspnœa, not only in the lower carbonic pressure in the alveolar air, but by the greater prevalence of acid in the blood. No doubt the low CO_2 pressure is due to the high value of other acids,* as also is the meionexy in the special class of cases.

We have endeavoured to get behind the mere fact of this acidosis, and have made some observations on the nature of the acid present. These, for the most part, have given negative results.

Respiratory quotient.

The respiratory quotients, as judged from the samples of alveolar air which were analysed, at first led us to look for some considerable metabolic disturbance. These quotients almost without exception were very low. Great caution must be exercised in interpreting any abnormalities in the respiratory quotient when based on an estimation of the alveolar air of untrained persons. We have already pointed out the uncertainty which exists with regard to the carbonic pressure, but the oxygen pressure in the alveolar air is even more uncertain, for a slight holding of the breath causes a fall in the oxygen pressure which is out of proportion to the rise in the carbonic acid pressure.

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* The high value of other acids producing hyperpnœa and a washing out of CO_2 from the lungs.

The following are the observations which we have made :—

Special cases of dyspnœa.

CASE		RESP. QUOTIENT.	DATE
1.	J. P. ..	·80, ·60	
2.	H. L. ..	·63, ·58	5.5.13
		·56	23.5.13
3.	G. S. ..	·54	
4.	D.	·69, ·77	
5.	F. C. ..	·65, ·61, ·63	31.1.13
		·62, ·56, ·56	5.2.13
		·56, ·67, ·64	14.2.13
6.	A. S. ..	·89, ·86	
7.	F. J. S. ..	1·0, ·86	14.5.13
		1·06, 1·00, ·88	21.5.13
9.	M. P. ..	·82, ·74	23.5.13
10.	H. P. ..	·62	

Simple cardiac dyspnœa.

13.	J. C. ..	·94	
14.	M. C. ..	·77, ·66, ·67	

Whilst these respiratory quotients are very low, the same is the case with some of those patients who had no dyspnœa, namely :—

Special controls.

1.	J. P. (2nd observation)	·81, 1·02
9.	M. P. (2nd observation)	·76
12.	R. J.	·66, 1·06

Controls.

16	H. H.	·73, ·78, ·83
17.	R. G.	·67, ·67
18.	W. S.	·83, ·87, ·86

It seems difficult therefore to attach any importance to our respiratory quotients as indicating any metabolic disturbances.

We have, however, sought for other symptoms of disordered metabolism on the chemical side. The appearance of acid in the blood prompted us to undertake observations of the lactic acid present, or rather the α oxyacid radicle. These observations are subsequently detailed.

Dealing with the cases as a whole, it may be serviceable to show in tabular form the relation of the degrees of dyspnœa to the value of K, and to the degree of acidosis, as estimated by the percentage saturation when exposed simply to 17 mm. oxygen pressure. In the accompanying table, the cases are arranged in six groups, according to the degree of distress as it was observed clinically. The smallest values of K and the lowest percentage saturations at 17 mm. O_2 are found in the group of urgently distressed cases, all of whom belonged to our "special group." The largest values of K and the highest percentage saturation are found at the end of the table. There is an evident and fair correspondence between the clinical and special observations ; here and there some discordance is noticeable, but no more than is to be anticipated in comparisons of this kind, for it is by no means an easy matter to compare the degree of distress in patients who present from

many points of view dissimilar clinical pictures, especially when such pictures are carried largely as mental impressions over considerable periods of time.

Our best comparisons of the relation of the clinical and special observations are to be found in those cases where the examinations were made from time to time in the same individual. When (as in CASES 2, 5 and 7), the degree of distress as witnessed at the bedside varied inappreciably, the value of K and the percentage saturation at 17 mm. O_2 pressure varied little or remained almost constant : where, on the other hand, the patients' condition either sensibly improved (as in CASE 1, 2nd observation, and in CASE 9, 2nd observation) or became evidently more serious (CASE 1, 3rd observation), then corresponding alterations in the values to which reference has been made were constantly seen. Thus, J. P. (CASE 1) when first examined, was orthopnœic and exhibited Cheyne-Stokes breathing : the rate of breathing during the hyperpnœic stage was 27 per minute : he was unable to suspend his breathing : he had a good deal of distress and suffered from attacks of nocturnal breathlessness. At this time, too, slight dropsy was present. The value of K was ·00018 in two observations. Within a few days his condition showed considerable improvement. He was no longer orthopnœic : Cheyne-Stokes breathing was seen only from time to time : the respiratory rate had fallen to 20 per minute : the breathing could be suspended for a few seconds : distress was absent : and the nocturnal attacks and dropsy had disappeared. Concurrently, K rose to ·00023. A month later, when admitted in a dying condition, having a return of orthopnœa periodic breathing and nocturnal attacks, being urgently distressed and having considerable dropsy and liver engorgement, K had fallen to ·00008—·00011.

Order of distressed breathing.

DYSPNŒA.	CASE.		RESP. RATE.	ACIDOSIS.	K.
1. Urgent distress	3.	G. S.	46	14″₀	·00012
	1.	J. P. (Obs. 3	41	?	·00008-·00011
	2.	H. L.	37-45	44″₀	·00012-·00019
	11.	C. S	38	46″₀	
	10.	H. P.	37	62-63°₀	·00016
	5.	F. C.	33	69″₀	·00014-·00016
	8.	J. S.		50-52″₀	
2. Moderate	7.	F. S.	39-42 (deep)	48-66″₀	·00020
	4.	D.	24-32 (deep)	55″₀	·00022
	1.	J. P. (Obs. 1)	27 (deep)		·00018
	14.	E. M. (cardiac	30-32 (no reserve)	71″₀	·00020
3. Slight to moderate	6.	A. S.	32-35 (shallow, no reserve)	60″₀	·00021
	9.	M. P. (Obs. 1)	33 (moderate, deep, no reserve)	61″₀	·00020
	15.	W. C (cardiac	24 (moderate, deep, no reserve)	77″₀	·00034
4. None resting	1.	J. P. (Obs. 2)	20 (some reserve)		·00023
	13.	T. C. (cardiac)	12-15 (no reserve)	84-96″₀	·00020
5. None with walking	12.	R. J.	19-2 (mod. reserve)	60″₀	·00033
	9.	M. P. (Obs. 2)	17 (some reserve)	74″₀	·00027
6. None with active exercise	16.	H. H.	17-2 (full reserve)		·00027
	17.	R. G.	24 (full reserve)	80″₀	·00028
	18.	W. S.	16 (full reserve)	74-6″₀	·00025

Similar changes occurred in the case of M. P. (*CASE* 9). When admitted to hospital, orthopnœa was present ; the respiratory rate was 35-40, there was little reserve, some distress, and nocturnal attacks were present. She also had a little dropsy. K at this time was estimated at ·00020. A month later, and at the end of her stay, the orthopnœa and nocturnal attacks had disappeared ; the respiratory rate was 24, and she was able to suspend the breathing for a considerable time : she was also able to walk slowly without developing breathlessness. By this time K had risen to ·00027, a normal figure. Simultaneously, the percentage saturation (at 17 mm. O_2 pressure, in the absence of CO_2) rose from 61% to 74% ; showing a decrease in the relative acidity of the blood (in respect of non-volatile acids). It is note-worthy that while the recovery of this patient was not complete, the percentage saturation remained relatively low (*i.e.*, 74%) ; it was also low in the special control case (*CASE* 12), the figure being 60%. Where there is partial recovery from breathlessness, but where an absence of complete reserve is noticed, signs of relative acidosis (non-volatile) remain to a slight extent.

Estimation of Urea Nitrogen, &c., and Chlorides in the Blood.

To estimate the quantity of *urea nitrogen* in the blood, we have employed two methods. The first method is that recently elaborated by Folin[10] and his co-workers. The second, or hypobromite, method is that of Moog,[13] as modified by Ambard and now used by Widal and other workers in Paris. We have also made use of the " Constant of Ambard " in a few cases. (A full account of the methods will be found in Weill's recent thesis[19].) Ambard, three years ago, showed that there is a mathematical relationship between the quantity of urea in the blood and urine ; that when the kidney debits urea at a fixed concentration (by debit is meant the output of urea per 24 hours as calculated from the output over a short period), the debit varies in direct proportion to the square of the concentration of the urea in the blood. The quotient of the urea of the blood divided by the square root of the urinary debit should be a constant figure.

The constant of Ambard is of special value in border-line cases where the quantity of urea in the blood is just within normal limits or slightly over ; a tendency to retention being expressed by an elevation of the constant.

One of our objects in estimating the urea of the blood was to ascertain whether the type of case which manifested the special form of dyspnœa was one in which urea is retained. It is now established, thanks to Widal and his school, that in a large percentage of cases of chronic interstitial nephritis there is a retention of urea ; such a retention being accompanied by anorexia, torpor, anæmia, pruritis and retinitis ; other signs, such as increased blood pressure and nocturnal dyspnœa may be present, but are not definitely associated with urea retention.

The quantity of urea nitrogen in the blood in a normal subject varies between ·014-·026$\%$, and the constant of Ambard lies between ·063 and ·08. In only three cases did we find an appreciable retention of urea. In *CASE* 1, the urea nitrogen in the blood stood at ·107$\%$; in *CASE* 3, in which red

granular kidneys were subsequently found, it stood at ·04%: both these patients died within 24 hours of the examination. In CASE 2, the urea nitrogen stood at ·036 at the second examination; the patient died a few weeks later. The constant of Ambard was also raised in a borderland case (CASE 7).

So far as the " special group " of cases is concerned, the presence of this functional defect of the kidney, namely retention of urea, cannot be regarded as a feature. In our series it seemed to occur only in the moribund.

The estimation of *non-protein nitrogen* (by Folin's method) was made from the same point of view. Folin[11] has shown that in normal subjects, the total non-protein nitrogen, like the urea nitrogen, is remarkably fixed in concentration, when the blood is drawn a definite time after a definite meal. In the investigation of hospital patients suffering from a variety of conditions, no such constancy was observed, the concentration, as a rule, being considerably higher. Folin's result has been confirmed, in part, quite recently by Farr and Austin in a preliminary report to the Society of Experimental Biology and Medicine, New York.

These investigators examined cases of cardio-vascular disease associated with renal congestion. In these cases there *was no rise* in the total non-protein nitrogen. In cases of chronic nephritis with albuminurea, cylindrurea and œdema, from ·040–·018 grammes of non-protein nitrogen were obtained per 100 cc. of blood, while Folin, in his normal cases, found from ·022–·026 grammes. Our results, in so far as they go, support the observations of Folin and of Farr and Austin. In none of the cases examined, with the possible exception of CASE 3, was there any marked departure from the normal. Many of the cases present figures which resemble the pathological cases of Folin not associated with definite kidney lesions. Even in CASE 3, no approach was made to the higher values observed by Farr and Austin.

The determination of *urea and rest nitrogen* in the blood (by Folin's method) was undertaken also for the purpose of ascertaining whether these substances were present in the blood in sufficient quantity to affect the reaction. Eppinger[7] took up this point in his study of acid intoxication. This investigator believed that in the presence of excess of acid in the blood, the part taken by ammonia and urea was that of a neutraliser, while the larger complexes, such as the polypeptides, was relatively unimportant. He claimed that in cases where the acid intoxication had been established, an excess of urea in the blood reduced the intensity of the syndrome, and that the introduction of an excess of amino acids or of urea tended to offset the effects of acid intoxication, experimentally produced.

In that group of renal cases characterised by a retention of chlorides, we sometimes note a dyspnœa of the Cheyne-Stokes type. This dyspnœa may follow upon some exertion on the part of the patient, oftener it occurs at night time or in the early hours of the morning, the patient being suddenly awakened by a feeling of suffocation, and sometimes it may have the appearance of a typical asthmatic attack. This form of dyspnœa was present in a number of our cases, so we thought it might be of some value to estimate

the chlorides in the blood.   The method employed was that used in Widal's
laboratories at l'Hôpital Cochin, and is a combination of Wenige's and
Charpentier Volhard's method (*Journ. d. Physiol. e. d. Pathol. gén., xiv, No. 4.*)
The normal quantity of sodium chlorides in the blood serum is ·562 grammes
per cent.   In our analyses only a small quantity of blood was at our disposal,
and in order to obtain enough serum, the blood was whipped and then centri-
fugalised.   In whipping the blood some red blood corpuscles were broken up,
hence our results are a little higher than those obtained by the Parisian workers.
The normal limits we have taken as varying between ·570 and ·575 per cent.

One of our cases showed some retention with ·610 grammes per cent. ;
she had ·078 grammes of urea, a not at all uncommon association.   Our other
cases varied between ·548 below the normal and ·585 slightly above normal.

We may safely conclude from the results obtained that the special type
of dyspnœa is not commonly accompanied by a retention of chlorides.

Investigation of the Nature of the Acidosis.

In order to elucidate the nature of the acidosis which is present in the
dyspnœic cases, determinations were made of the lactic acid in the blood
and urine, and of nitrogen, ammonia and excess of acid in the urine.

Lactic acid was estimated by the method devised by Ryffel.[16]   This
consists in decomposing the lactic acid to acetaldehyde by heating with
about 50 per cent. sulphuric acid in a current of steam at 155 C., and
estimating the resulting aldehyde, after redistillation from alkaline solution,
by comparison of the colour obtained on the addition of standard Schiff's
reagent (rosaniline hydrochloride solution bleached with sulphur dioxide)
with the colour of standard solutions containing dilute formaldehyde and
Schiff's reagent.   As the reagent varies somewhat, the method was
standardised periodically by performing estimations on known solutions of
calcium lactate.   From blood the proteins were removed by mixing with
200 cc. of 0·5 per cent. acid potassium phosphate solution and coagulating
by heat.   The coagulum was thoroughly washed by boiling with water and
the combined filtrate rendered alkaline with sodium carbonate and evaporated
to small bulk on the water bath before being used for the distillation.   The
urines were treated with basic lead acetate and ammonia to render glycuronic
acid, proteins, &c., filtered and evaporated, then employed directly for the
distillation.   This method has two great advantages ; preliminary extraction
with ether and consequent loss are avoided, and the amount of material
required is small, results which have an error of less than one-tenth being
obtainable with 0·0025 grm. lactic acid, so that no more than 15 cc. of blood
were necessary.   Schiff's reagent is distinctive for aldehydes so that only
those substances are included in the estimation which yield aldehydes under
the conditions of the distillation.   These are a hydroxy fatty acids, of which
lactic acid is the only one known to occur in the body, pentoses and glycuronic
acid, which do not occur appreciably in the blood and as far as the urine is
concerned are removed by the basic lead acetate and ammonia.   Oxy-butyric
acid being a β acid does not react in this way.

The total nitrogen of the urine was estimated by Kjeldahl's method, the acidity of the urine by Folin's method, and the ammonia by the formaldehyde method.

Lactic acid in the blood in relation to acidosis.

The control cases, Nos. 16 to 19, in which there was no acidosis, dyspnœa or cyanosis, gave results varying from 0·016 to 0·036 grm. lactic acid per 100 cc. blood. Previous values determined on the blood of six normal individuals at rest had ranged from 0·012 to 0·016 grm. per 100 cc., but these were all much younger individuals, so that it would appear that there is a tendency for the lactic acid of the blood to rise as age advances. Of the cases which gave evidence of acidosis two (CASES 1 and 3) were exceedingly ill at the time the blood was taken and died within 24 hours. The lactic acid of the blood was distinctly high, 0·091 and 0·056 grm. per 100 cc. respectively, but the increase above the normal was evidently inadequate to account for the acidosis, which was equivalent to 0·15 grm. lactic acid. The urea of the blood was also distinctly above normal.

The other cases of acidosis in which the lactic acid was determined gave results varying from 0·016 to 0·030, so that there was no evidence of an increase of lactic acid in the blood corresponding to the acidosis. Moreover in CASE 9 the lactic acid of the blood was practically the same when she had dyspnœa and acidosis and when these had disappeared.

Lactic acid in urine.

The quantities of lactic acid in the urine were all small, but the urine of CASES 1 and 3, whose blood contained excess of lactic acid, was not examined. The results obtained from the control cases varied from 0·016 grm. to 0·121 grm. per diem, the larger quantities corresponding to the higher values in the blood. The cases with acidosis gave from 0·025 to 0·065 grm. per diem, so that in the cases examined there was no evidence of an abnormal excretion of lactic acid.

Acids in urine.

Rothera's[15] test for acetone and acetoacetic acid was applied to all the urines and found negative in every case. The test is very sensitive but does not give a result with the small amount of acetone bodies present in normal urine. As oxybutyric acid has never been found in appreciable quantities in the absence of the other acetone bodies, we may conclude that the acetone bodies were not present in excess in any of the urines.

The control cases gave ammonia nitrogen 0·21 to 0·47 grm. per diem, acidity 132 to 285 cc. $\frac{N}{10}$ per diem. Folin's maximum values on a standard diet rather poor in bases were : ammonia nitrogen 0·85 grm. per diem, ratio to total nitrogen 5 per cent., acidity 669 cc. $\frac{N}{10}$ per diem. Excluding CASE 5, the cases with acidosis gave ammonia nitrogen 0·18 to 0·60 grm. per diem, acidity 99 to 402 cc. $\frac{N}{10}$ per diem. CASE 12, whose dyspnœa had passed off and who showed only very slight acidosis gave ammonia nitrogen 0·66 and total acidity 667 cc. $\frac{N}{10}$ per diem. In these cases there is clearly no connection between the acidosis and increased excretion of total acid or ammonia.

CASE 5, however, gave ammonia nitrogen 1·35 grm. per diem, ratio to total nitrogen 9·3 per cent., total acidity 464 cc. $\frac{N}{10}$ per diem, a quantity of ammonia distinctly in excess of the normal. Folin's organic acidity was accordingly determined on this urine, but the result, 170 cc. $\frac{N}{10}$ per diem, did not show the presence of an abnormal amount of organic acid.

Discussion of results.

Acidosis, due to the presence of an abnormal excess of acids other than carbonic acid over the bases of the blood, may be due either to excessive formation of acid products of incomplete oxidation, such as lactic acid and acetoacetic acid, or to an alteration in the behaviour of the kidneys in excreting the acids and bases that result from normal metabolism, whereby the balance of these bodies is kept at an abnormally acid level.

The acidosis of hard exercise[3] with the resulting dyspnœa which continues after the exercise ceases, so that the alveolar carbon dioxide falls below normal,[5] is due to accumulation in the blood of lactic acid formed in the muscles.[17] The acidosis of diabetic coma[1] is similarly due to the production of large quantities of organic acids, principally acetoacetic, oxybutyric and lactic acids. In both these instances the kidneys are reacting normally in excreting acid, but fail to keep pace with the unusual production of acid.

During residence at an altitude of 10,000 feet or more the alveolar carbon dioxide falls progressively until accommodation is well established.[6] An excess of non-volatile acid is retained in the blood to compensate for this loss of carbonic acid with the result that the dissociation curve of the blood is displaced slightly in the acid direction.[1] The slight increase of lactic acid which is observed in the blood is not adequate to account for more than a small part of this retention of acid and no increase of lactic acid is excreted in the urine, so that this change appears to be an instance of the second cause of acidosis, namely, altered excretion of acids and bases by the kidneys, which is beneficial at high altitudes, as the pressure of oxygen in the lungs is thereby increased.[2]

The results described above show that the acidosis observed in our cases is not due to an increase in the lactic acid of the blood, except to a partial extent when the patient is in extremis. Further no evidence of the formation of an abnormal amount of any organic acid is to be obtained from examination of the urine, so that this acidosis appears to be another instance of the same phenomenon of retention of acids in excess of bases which is shown during residence at high altitudes. The retention of acid might in this case be due either to failure of the kidneys in respect of excretion of acid, or to a change of behaviour more strictly comparable to that at high altitudes. If the former were the case, the condition would admit of simple treatment by giving a diet rich in bases so as to prevent the formation of excess of acid in metabolism. The matter is being further investigated, but the results of the urea determination do not indicate failure of secretory power except in the extreme cases.

In the following table the results of the determinations of excess of acid, lactic acid, urea and total non-protein nitrogen in the blood are compared.

Case.	Excess of acid expressed as lactic acid per cent.	Actual total lactic acid per cent.	Urea N. (Hypobromite) per cent.	Urea N. of F... per cent.	Non-protein N. (Folin) per cent.
Acidosis & Cheyne-Stokes Respiration.					
1.	0·15	0·091	0·11		
2.	0·05	0·030	0·015		
3.	0·15	0·056	0·040	0·043	0·046
4.	0·05	0·025	0·015	0·017	0·021
5.	0·01	0·016	0·017		
6.	0·02	0·027	0·022	0·022	0·036
7.	0·04	0·021	0·023	0·015	0·024
		0·017	0·023		
Acidosis. Not Cheyne-Stokes					
9.	0·02	0·024	0·018		
	0·00	0·025	0·020	0·032	0·025
10.	0·02	0·026	0·017	0·017	0·020
12.	0·02	0·023		0·023	0·035
Cardiac Dyspnœa.					
13.	0·00	0·019	0·018	0·022	0·026
14.	0·00	0·027	0·018	0·017	0·032
15.	0·00	0·033	0·019	0·021	0·033
Simple Controls.					
16.	0·00	0·020	0·023	0·023	0·034
17.	0·00	0·036		0·017	0·021
18.	0·00	0·030		0·027	0·035
19.	0·00	0·016			

Conclusions.

1. Many patients who are the subjects of cardiac disease exhibit considerable breathlessness but they show no cyanosis or they lack an equivalent cyanosis. In these patients the dyspnœa is evidently not the result or not entirely the result of deficient aeration of the arterial blood, nor is the dyspnœa due to an accumulation of CO_2 caused by stasis. It is due, as the present observations show, to a condition of acid intoxication. The nature of this acidosis is similar to that found in normal people at high altitudes ; it is not the result of excess of CO_2 in the blood, neither is it due to excess of α oxy-acid radicles (except in some measure in moribund patients) or β oxy-butyric acid, as in diabetes.

2. This form of acidosis, when exhibited by patients, occurs usually in elderly subjects who have lesions in the heart, arteries and kidneys in varying degrees. It is often accompanied by periodic breathing of the Cheyne-Stokes type and by attacks of intense dyspnœa, meriting in some cases the term "uræmic," in other cases the term "cardiac asthma." It is usually accompanied also by wasting, a rapid heart action (80-100) or a perverted heart mechanism, by signs of cardiac failure, by signs of renal derangement and a subnormal temperature. High blood pressure is common, retention of urea or chlorides may be present but is found infrequently.

3. It is probable, though it cannot be held as finally proven, that there is no essential difference between "cardiac" and "renal" asthma, so called ; and that the dyspnœa of the cardiac cases is in reality due ultimately to renal defects.

4. Considering all forms of dyspnœa, it seems probable that, where the breathlessness is great and where neither anæmia nor cyanosis is conspicuous, such dyspnœa arises in the majority of cases from acid intoxication.

5. The cause of the dyspnœa which we describe is in sharp contrast to that in the pure cardiac cases where excessive accumulation of CO_2 in the blood sufficiently accounts for its acid reaction and the respiratory stimulus.

	Date.	Age.	Etiology.	Duration	Heart.	Arteries.	Urine and Kidneys.
Acidosis and C.-S. breathing. 1. J. P., ♂	1.3.13	69	" Slight pneumonia" 18 m. before	18 months.	Enlarged (610 gms.). Chambers dilated. Valves normal. Auricular fibrillation. Bundle branch lesion. Rate 80. Coronary disease.	General atheroma. B.P. 130-160	1,100-2,500 c.c. Acid. No alb. or casts. Wht. 390 gr., Slight fibrosis. (7.4.13)* Dark, scanty.
2. H. L., ♂	5.5.13	66	nil	2 years.	Enlarged (495 grms.). Chambers dilated. Mitral regurgitation. Extrasystoles ; alternation. Rate 96. Coronary disease ; angina ; muscle fatty.	General atheroma. B.P. 150.	300-500 c.c. Acid : 7"/₀₀ alb., gran. casts. Urobilin in excess. No retinitis. Wht. 326 gr., Scattered fibrosis.
3. G. C. S., ♂	28.4.13	67	nil	2 years.	Enlarged (650 grms.). Dilated chambers. Mitral regurgitation. Auricular fibrillation. Rate 110-120.	General atheroma. B.P. 160.	Acid, 1,020, alb. and gran. casts. Wht. 270 gr. ; red granular (advanced).
4. D., ♂	10.5.13	57	nil	1 year.	A little enlarged. No murmurs. Heart-block, extra-systoles, alternation.	Apparently healthy. B.P. 200-210.	650-2,000 c.c., acid ; alb. and gran. casts. No retinitis.
5. F. C., ♂	19.1.13	53	nil	2 years.	Enlarged (425 grms.). Chambers dilated. Valves normal. Rate 100. Coronaries very calcareous.	Some atheroma. B.P. 180.	450-1,500 c.c.; acid, 1,032-14; alb. ; no casts. Sl. excess of urobilin. Wht. 400 gr., fibrosis and lymphocytosis
6. A. S., ♂	19.5.13	57	Rh. Fever	2 years.	Enlarged. Aortic disease. Paroxysmal tachycardia ; heart-block. Angina. Rate 60-80 and 120-160.	Tortuous and thickened. B.P. 150-200.	1,100-2,500 c.c. ; 1,015 ; acid ; alb. and gran. casts. Excess of urobilin.

* This date applies to

POST MORTEM.

Breathing.	Colour.	Hbo. and red cells.	Remarks.
Orthopnœa; C.-S. breathing; gasping; rate 27; no reserve; nocturnal attacks. (7.3.13).*	Very slight cyanosis of lips.	102% 4,860,000	Veins full; liver enlarged; signs of small effusions into pleuræ; slight dropsy
No orthopnœa; C.-S. breathing only occasional; easy while resting; rate 20; some reserve. No nocturnal attacks. (12.3.13).*	Little or no cyanosis.		Veins full; liver slightly enlarged; lungs clear; no dropsy.
Orthopnœa; C.-S. breathing gasping; v. restive; no reserve; distress urgent.	Moderate cyanosis of lips and ears.		Bronchitic signs; pleural effusions; liver enlarged; considerable dropsy.
Orthopnœa; C.-S. breathing. Rate 36; v. restive; no reserve; v. distressed; nocturnal attacks. (5.5.13).	Slight cyanosis	82% 3,300,000	Veins full; liver much enlarged; ascites, dropsy.
Same. (23.5.13).	Slight cyanosis.	90%	Same.
Orthopnœa; C.-S. breathing; gasping; restive; v. distressed; rate 46. No reserve. Nocturnal attacks.	Slight cyanosis of lips; deeper of ears, tongue and fingers.	75% (p.m.)	Veins full; liver much enlarged; general bronchitis; pleural effusions; ascites, dropsy.
No orthopnœa; C.-S. breathing; gasping; restive and distressed; rate 35-40. Nocturnal attacks.	No cyanosis.	90% 4,790,000	Drowsy. Veins full; liver not enlarged; a little bronchitis; no dropsy.
Orthopnœa; C.-S. breathing; gasping; restive and v. distressed; rate 35. No reserve. Nocturnal attacks. (29.1.13).	Very slight cyanosis.	60% 3,980,000	Drowsy. Liver a little enlarged; rhonchi and creps. at bases; slight œdema of ankles.
Much the same; evening attacks very severe. (5.2.13).	Very slight cyanosis.	80% 3,780,000	Same. Pleural effusion on right side.
Same. (14.2.13).	Very slight cyanosis.		Same.
Sl. orthopnœa; C.-S. breathing; not much distress; rate 33. Nocturnal attacks.	Slight cyanosis of lips; none of cheeks and ears.	95% 6,140,000	Veins full; liver enlarged; signs of small pleural effusions; dropsy of feet.

all succeeding entries.

ALVEOLAR AIR AND BLOOD-GAS ANALYSES.

Alv.CO_2 in mm.	Alv. Quotient (corrected).	Test for Meloxy.				at. at 17 mm. O
		O in mm	CO in mm	Sat.	K	
33·8 29·5	·45 ? ·78 ·59	37 34	31	60% 55%	·00018 ·00018	
25 31	·80 1·00	33·3	22	59·5%	·00023	
26 (approx)		31·9 37·7	26·9	31·5% 50·2%	·000082 ·00011	14%
31 31	·63 ·58	30	29	38·5%	·00013	44%
28·6	·56	29·5	27	47·5% 48%	·00019	43%
13	·54	31	9	41%	·00013	14%
27 30	·69 ·77	39·5	30	69%	·00022	55% (14.5.13).
28 29	·42 ·68	16 22·5	30	14% 26%	·00012 ·00015	69%
25 27·4 27·9	·60 ·55 ·58	27 40	27	27% 63%	·00010 ·00016	
31 27 31	·64 ·66 ·67					
29 26	uncorrected ·89 ·86	43	28	72%	·00021	60%

	BLOOD.					URINE.					

N (Foam)			Urea N (hypobrom.) %	Chlorides %	Lactic Acid %	Volume in c.c.	Lactic Acid % and gr. p.d.	Total N % & gr. p.d.	NH Nitrogen % and gr. p.d.	NH Total N and g.	Total Acid as N
Non-protein Nitrogen %	Urea Nitrogen %	Rest Nitrogen %									
			·107		·091						
			·015 $K*$— ·087		·030	385	·0062 ·024	1·43 5·51	·0693 ·267	4·8	279
			·036	·610							
·0464	·0434	·003	·040		·0565						
·0208	·0171	·0037	·015		·025	657	·0044 ·029	1·30 8·54	·0886 ·582	6·8	239
			·017		·016	1000		1·45 14·5	·135 1·35	9·3	464
·0364	·0218	·0146	·022		·0275	1445	·0042 ·060	·665 9·41	·0123 ·178	1·85	99

* K = Ambard's " constant."

	Date.	Age.	Etiology.	Duration	Heart.	Arteries.	Urine and Kidneys.
7. F. J. S., ♂	14.5.13	63	nil	9 months	Enlarged (626 grms.). Chambers dilated. Valves normal. Rate 90-120. Coronaries calcareous. Muscle v. fatty.	Tortuous and thickened. B.P. 200-220.	Quantity reduced ; high colour ; alb. and gran. casts. Wht. 270 gr., considerable fibrosis.
8. J. S., ♂	7.3.13	64	nil	? 6 weeks	Enlarged (695 grms.). Chambers dilated. Valves normal. Rate 72-100. Coronaries rigid.	General atheroma. B.P. 190-200.	Alb. present. Rt. kidney advanced arterio-sclerotic ; left, considerable fibrosis.
Acidosis without C.-S. breathing. 9 M. P. ♂	23.5.13	61	nil	2 months	Enlarged. No murmurs. Rate 80-100. Extrasystoles. Gallop rhythm.	Thickened. B.P., 170-200.	Quantity increased. Acid. Alb. but no casts. Sl. excess of urobilin.
10. H. P., ♂	28.4.13	50	? Typhoid Fever	? 20 years.	Enlarged. Valves normal. Rate 84-125. Gallop rhythm.	Thickened. B.P. 170-200.	350-1,100 c.c.; 1,010-20 ; alb. and gran casts. No retinitis. Uric acid ·098%.
11. C. S., ♂	28.4.13	54	Rh. Fever	4 years.	Enlarged (460 grms.). Mitral stenosis ; aortic disease. Usually auricular fibrillation. Reg. paroxysm at 180-200.	General atheroma.	Quantity reduced. High colour. Wht. 255 gr., little fibrosis apart from old infarcts.
Special control 12. R. J. ♂	26.5.13	56	? " Influenza"	2 days.	Enlarged. Mitral regurgitation. Rate 76-106.	Tortuous and thickened. B.P. 180-200	900-2750, c.c., alb. and gran. casts. No retinitis.
Cardiac Dyspnœa. 13. T. C., ♂	21.4.13	49	" Influenza "	4 years.	Enlarged. No murmurs. Paroxysmal tachy-cardia. Alternation ; extrasystoles. Rate 90 and also 160.	Thickened. B.P. 150-130.	500-3,600, c.c. Acid 1,030-10; alb. and gran. casts. No retinitis.

POST MORTEM.

BREATHING.	COLOUR.	HBO. AND RED CELLS.	REMARKS.
Orthopnœa; C.-S. breathing ; restive and distressed ; rate 40 ; no reserve. Nocturnal attacks. (14.5.13).	Slight cyanosis of lips, ears and fingers.	100%	Veins a little full ; liver enlarged ; pleural effusion on right side ; dropsy.
Same. (21.5.13).	Same.	100%	Weaker.
Orthopnœa ; C.-S. breathing ; restive and v. distressed ; rate rapid.	Slight cyanosis.		Delirious and semi-comatose ; veins full ; liver and spleen enlarged ; Pleural effusions ; dropsy.
Orthopnœa ; irreg. breathing ; rate 30-40 ; little reserve ; not much distress. Nocturnal attacks. (23.5.13).	Very slight cyanosis of lips and tongue.	90%	Liver slightly enlarged ; a few creps. at lung bases ; dropsy.
No orthopnœa ; reg. rate 24 ; a good deal of reserve. Can walk without dyspnœa. No nocturnal attacks. (24.6.13).	Same.	84%	No dropsy.
Orthopnœa ; rate 39 reg. ; a good deal of distress ; no reserve. Nocturnal attacks.	Slight cyanosis of lips ; deeper in cheeks and ears.	88% 4,390,000	Veins full ; liver a little enlarged.
Orthopnœa ; laboured rate 37 ; very distressed ; no reserve.	Moderate to deep cyanosis of lips, cheeks and ears.		Veins full ; liver greatly enlarged ; pleural effusions ; œdema of lungs ; ascites and dropsy.
No orthopnœa ; breathing free at 18 per minute ; a good deal of reserve ; has had dyspnœa and C.-S. breathing.	No cyanosis.	4,980,000	Veins full ; liver a little enlarged ; a little bronchitis ; no dropsy.
No orthopnœa ; free while resting ; irreg. ; rate 15. Little or no reserve.	Very slight cyanosis of lips, ears and fingers.	80% 3,650,000	Veins full ; liver enlarged ; emphysema ; a few râles ; no dropsy.

ALVEOLAR AIR AND BLOOD-GAS ANALYSES.

Alv.CO$_2$ in mm.	Alv. Quotient (corrected).	Test for Meionexy.				Sat. at 17 mm. O$_2$
		O$_2$ in mm.	CO$_2$ in mm.	Sat.	$K =$	
33·6 33·6 30·5	1·0 ·86 ·81	27	32	$> 43\%$	$< ·00020$	48%
32 40·6 33	1·06 1·00 ·88	28·5	36	46%	·00020	66%
						50-52%
36 33	·82 ·74	31·2	36	51% 52%	·00020	61%
40 41	·76	26·8	39·4	51% 49%	·00027	74%
27	·62	28	29	40%	·00016	63% 62%
						46%
27·6 28	·60 1·08	30	27	60% 61%	·00033	60%
46 47	·95	42·5 43·5	45 46	69·5%	·00020	84% 96%

	BLOOD.						URINE.				

| N (Folin) | | | Urea N (hypobrom) % | Chlorides % | Lactic Acid % | Volume in c.c. | Lactic Acid % and gr. p.d. | Total N % and 1 gr. p.d. | NH₃ Nitrogen % and gr. p.d. | NH₃ Total N % and gr. p.d. | Total Acid as N 1/10 |
Non protein Nitrogen %	Urea Nitrogen %	Rest Nitrogen %									
·0236	·0152	·0184	·023 K ·094		·021	462	·0055 ·025	1·36 6·31	·101 ·467	7·4	242
			·023	·548	·017	605	·0054 ·037	1·13 6·84	·069 ·417	6·1	235
			·018	·558	·024						
·0322	·0247	·0075	·020	·574	·025	500	·0037 ·0185	·954 4·77	·033 ·164	3·4	274
·0196	·0168	·0028	·017 K ·073		·022+ and ·026	842	·0061 ·0514	1·49 12·55	·0714 ·601	4·8	402
·0352	·0227	·0125			·023	1135	·0057 ·065	1·38 15·7	·0580 ·66	4·2	667
·0260	·0224	·0036	·018 K ·127		·019	2055	·0031 ·064	·699 14·36	·0411 ·844	5·88	179

	Date.	Age.	Etiology.	Duration	Heart.	Arteries.	Urine and Kidneys.
14. E. M.,	4.6.13	29	Chorea	11 years	Much enlarged. Mitral stenosis. Auricular fibrillation. Rate 100.	Seem normal. B.P. 90-100.	Quantity reduced. Acid. 1,026-38. Alb., no casts. Urobilin in great excess.
15 W. C.,	2.6.13	44	Rh. Fever	5 weeks	Enlarged. Mitral regurgitation. Auricular fibrillation. Rate 110.	Thickened B.P. 160-190.	500-1,400 c.c. Acid. alb., no casts. Urobilin in excess.
CONTROLS. 16. H. H.	9.6.13	45	Convalescent Admitted for gastric symptoms.		Normal. Rate 88.	A little tortuous. B.P. 134.	Normal.
17. R. G.,	11.6.13	56	Convalescent Operation for appendicitis.		Normal. Rate 78.	Some thickening.	Normal.
18. W. S.,	20.6.13	61	Convalescent Operation for fistula-in-ano		Normal. Rate 62.	Seem normal.	Normal.
19. S. G.,	18.6.13	54	Convalescent Fractured patella		Normal. Rate 58.	Seem normal.	Normal.

POST MORTEM.

Breathing.	Colour.	Hbo. and red cells.	Remarks.
Orthopnœa; breathing laboured, irreg., rate 33. No reserve.	Deep cyanosis of lips, cheeks, tongue, ears and fingers.	92·5% 4,420,000	Veins full; liver greatly enlarged; a few creps. at lung bases; dropsy.
No orthopnœa; rate 24; very slightly irregular. No reserve.	High colour; slight or moderate cyanosis of lips, cheeks, ears and fingers.	88% 5,010,000	Veins a little full; liver enlarged; no dropsy.
Resp. rate 17. Full reserve.	High colour; slight cyanosis of lips, cheeks, fingers and ears.	102%	
Resp. rate 24. Full reserve.	Very slight cyanosis of lips; none of tongue, cheeks or ears.	90%	
Resp. rate 16. Full reserve.	A mere trace of cyanosis of lips; none of cheeks, ears or fingers.	106%	
Resp. rate 18. Full reserve.	Very slight cyanosis of lips only.	95%	

ALVEOLAR AIR AND BLOOD-GAS ANALYSES.

Alv.CO$_2$ in m.m.	Alv. Quotient (corrected).	Test for Meionexy.				Sat. at 17 mm. O$_2$.
		O$_2$ in mm.	CO$_2$ in mm.	Sat.	$K =$	
39 43 41	·77 ·66 ·67	31	40	49% 55%	·00021	71%
(2.6.13) 38 (3.6.13) 37 24	·73 ·78 ·86	29·3	38	54% 58·6%	·00034	77%
40 38 38	·73 ·78 ·83	34·4	36·3	61·2% 62·5%	·00027	69% 75% not reliable.
35·5 36·8	·67 ·67	30·1	35·2	54% 58%	·00028	80%
41 41 39	·83 ·87 ·76	35·8	38	64·5% 66%	·00025	74·6%
not reliable.						70% 71%

BLOOD.						URINE.					
N (Folin)			Urea N hypobrom.	Chlorides	Lacti- Acid	Volume in c.c.	Lactic Aid % and gr. p.d.	Total N % and gr. p.d.	NH Nitrogen , and gr. p.d.	NH, Total N , and gr. p.d.	Total Acid as N 1 5
Non-proteid Nitrogen %	Urea Nitrogen %	Rest Nitrogen %									
·0324	·0172	·0152	·018	<u>·580</u>	·027*	552	·0044 ·024	1·19 6·55	·0587 ·224	4·95	168
·0327	·0206	·0121	·018	<u>·571</u>	·033*	1200	·0022 ·026	·636 7·63	·0395 ·474	6·2	144
·0338	·0235	·0103	·023 K -·125	<u>·585</u>	·020*	900	·0034 ·0304	1·033 9·30	·023 ·211	2·3	285
·0206	·0175	·0031			·036	1210	·010 ·121	·841 10·18	·039 ·47	4·7	282
·0346	·0267	·0079			·030*	1130	·0095 ·107	·598 6·76	·0235 ·265	3·9	132
					·016*	1055	·0015 ·016	·507 5·35	·019 ·206	3·8	150

* Quantity of blood examined was small.

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DETAILED ACCOUNTS OF THE PATIENTS.

CASE 1. (*Acidosis and C.-S. breathing.*)

A case of cardiac, arterial and renal disease in which there was dyspnœa, but little cyanosis, accompanied by Cheyne-Stokes breathing and suffocative attacks at night.   Special examinations were made on three occasions during the patient's illness ; acidosis was found ; the result afforded on each occasion a complete explanation of the degree of respiratory distress observed at the time. Death occurred with signs of cardiac and renal failure (retention of urea and hydroxy-acids developed).

J. P., a hotel keeper of 69 years, was admitted to University College Hospital in the autumn of 1911, complaining of breathlessness, feelings of faintness and swelling of the legs.

History (17.11.11).   He remembers no past illness.   Beer has been drunk in moderation ; he has smoked heavily.

Present illness.   His heart is stated to have been weak since an accident to the spine in 1907. A severe " cold " was contracted in October, 1911, and he laid in bed with slight pneumonia for some weeks.   Since this illness the symptoms have increased ; he now complains of great breathlessness upon slight exertion, attacks of breathlessness at night and general lassitude ; frequent giddy attacks ; and puffiness of the eyes and swelling of the legs.

The condition at this admission was so similar to that observed on a later occasion that a short description of it will suffice.   He showed conspicuous breathlessness, a slight or moderate amount of cyanosis, signs of cardiac failure and renal insufficiency.   During his stay, Cheyne-Stokes breathing was often observed, he was frequently delirious and on several occasions comatose. Although his life was despaired of, he made a slow and partial recovery.

1.11.12.   He was re-admitted on this date for similar symptoms and wasting ; they had increased in intensity for three weeks.   His condition was the same as in October, 1911.   He improved during his stay but was again re-admitted on March the 1st, 1913, with the old symptoms.

The condition (1.3.13).   A description of the signs found on this day may stand also for that of previous dates.   A well-built man, who lies propped in bed with pillows.   The *facies* are grey, he is pale and slightly cyanosed.   The *breathing* is gasping, and shows periodic waxing and waning in depth with long apnœic pauses.   He cannot hold his breath voluntarily, and the slightest movement in bed increases his distress.   He is restive.

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* The detailed report of the Monte Rosa Expedition of 1911 is in course of preparation and will be communicated for publication to the Phil. Trans. of the Royal Society.

Analysis of respiratory curves.

	HYPERPNŒA.		HYPOPNŒA.	
	DURATION.	RATE.	DURATION.	RATE.
6.3.13 ..	18 secs.	27 p.m.	18 secs.	26 p.m.
5.4.13 ..	63 ,,	41 ,,	22 ,,	0 ,,

The *heart* is enlarged (limits from mid-line, 1½ and 5½ inches, apex beat obscured by lungs). There is no sign of valve disease ; the first sound is sometimes reduplicated, forming a gallop rhythm, at the apex. Fibrillation of the auricles is always present and the electrocardiograms indicate also defective conduction in the right branch of the *A-V* bundle. The heart's rate varies around 80 per minute. *Arterial system.* The pulse is continuously irregular and feeble ; the blood pressure varies between 130-160 mm. Hg. (most forcible beats). The arteries of the limbs are thickened. *Venous reservoirs, &c.*. The veins are full and pulsate freely ; there are no signs of auricular contractions. The liver is palpable below the rib margin ; slight œdema of the ankles is present. The *kidneys*. The urine varies in quantity between 1100 and 2500 c.c. per diem (1st to 31st of March, 1913) ; the reaction is always acid ; sp. gr. 1010-1012 ; albumen and casts are not to be found. *Lungs.* Impairment of resonance and weak breath sounds are noted at the bases.

Course. The urgency of the breathing decreased within a few days of admission. On the 7th of March the periodic breathing was no longer continuous ; on this day apnœa was seen only occasionally ; though still distressed the condition had ameliorated. By the 9th the periodic breathing was almost confined to the hours of night. On the 12th the periodicity was still rarer and during the day the breathing was natural while the patient rested. The patient was discharged on March the 30th much improved. During his stay the temperature was subnormal, varying between 97° and 98° Fahr..

Further course. 3.4.13. He was readmitted very decidedly worse. Orthopnœa, laboured breathing of the periodic type, signs of returning stasis, an increase in the amount of cyanosis were present. The urine was scanty, dark and of high density. Over the bases of the lungs numerous crepitations were heard. For several days the condition remained unaltered. On the 7th his condition was grave, cyanosis deepening, and the breathing becoming more gasping and less effective. Albumen was found in the urine. He died in the evening without further warning. During this brief stay the urine varied between 100-900 c.c. per diem ; the blood pressure between 138 and 116 mm. Hg.. The heart's action remained unchanged. The temperature remained subnormal.

Post mortem, 8.4.13.

Dropsy is present in the legs ; the pleural cavities contain each 1 pint of clear fluid ; there is also an excess in the pericardial and peritoneal cavities. The *lungs* are slightly emphysematous, the bases congested and œdematous. The *heart* and vessels weigh 610 grammes (muscle of the R.V. 62·0 ; of the L.V. 138·0 ; of the septum 32·5 grammes). The auricles and ventricles are dilated, the latter are overloaded with fat, and the muscle seems fatty. The right coronary orifice is narrowed, the vessels are tortuous though wide and their walls atheromatous. With the exception of small calcareous deposits at the bases of the aortic segments, and considerable dilatation of the tricuspid orifice, all the valves are normal. The *aorta* and larger vessels show general athero-sclerosis. The *kidneys* weigh 390 grammes and are congested ; the capsules strip easily, tearing a little ; the kidney surface is finely granular. Cortex and medulla are reduced in relation to the general size of the organ ; the pelvis with its fat is wide. Microscopically the vessels are engorged and show some medial thickening. A few hyaline Malpighian corpuscles are seen ; there are areas over which scattered lymphocytic collections and slight fibrosis are found. The epithelium of the convoluted tubules is ragged and appears to be partially disintegrated. The tubules are distended. The *liver* and *spleen* are congested and friable.

CASE 2. (*Acidosis and C.-S. breathing.*)

A case of cardiac and renal disease in which persistent dyspnœa, accompanied by Cheyne Stokes breathing and suffocative attacks at night, were prominent features. Cyanosis was never conspicuous. Special blood examinations explained the respiratory distress. Death occurred with signs of cardiac and renal failure ; (retention of urea developed).

H L., a married woman of 66 years, was admitted to the City of London Hospital on April the 22nd, 1913, complaining of great distress of breathing and other symptoms.

History (22.4.13). There is no memory of past illness. She has had one child and no miscarriages. The illness began two years ago with shortness of breath and this has increased; it has been continuous and is increased by exertion. For several weeks frequent vomiting and attacks of severe pain, confined to the sternal region, have been prominent. A cough is complained of; attacks of palpitation and giddiness are common. She is wasting rapidly. Sleep is very disturbed; she wakes repeatedly at night feeling suffocated. Frequent and excessive micturition has been present.

The condition (5.5.13). A frail woman (weight 8 stone 4 lbs.) who sits propped in bed with pillows; a curious sour odour is present in the room. The skin is discoloured; the conjunctivæ are yellow; cyanosis is not prominent. The *breathing* is hissing and periodic (Fig. 6). The hyperpnœic phase is accompanied by great distress and restiveness.

Analysis of respiratory curves.

	HYPERPNŒA.		HYPOPNŒA.	
	DURATION.	RATE.	DURATION.	RATE.
1.5.13 ..	80	37-45 p.m.	25	33 (v. irreg.) p.m.
14.5.13 ..	70-80	28-45	17-31	0
22.5.13 ..	60-80	40	30-40	0
27.5.13 ..	70-72	33-45	20	0
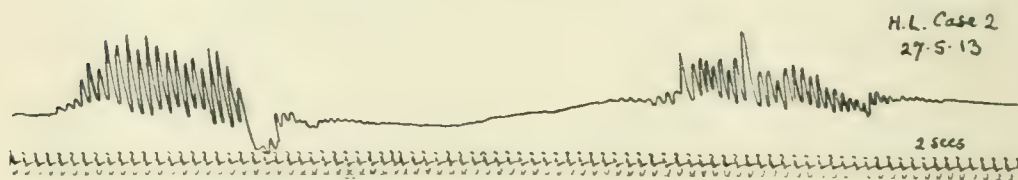
Fig. 6.

Towards the end of the hyperpnœic phase, the lips and tongue are pink or very slightly cyanosed, during the apnœic periods the lips and tongue become slightly cyanosed. The hands are cold and tinged with blue. The *heart* is considerably enlarged (apex beat in the 7th interspace, ant. axillary line; limits of dulness 1¾ and 7 inches from the mid-line). A systolic murmur is heard at the apex; the 2nd sound is intensified and reduplicated at the aortic cartilage. The normal auriculo-ventricular contraction sequence is present, interrupted by extrasystoles and these are followed by alternation. *Arterial system.* The pulse rate varied between 58 and 132 per minute (during the illness), lying usually between 80 and 96. Faster rates prevailed towards evening. The blood pressure is 150 mm. Hg.. The arteries seem thickened.

Venous reservoirs, &c. The veins are full and pulsate freely. The liver is easily palpable, the edge is hard and feels nodular. Dropsy is present in the legs and there are signs of some ascites. *The kidneys.* The urine is acid; sp. gr. 1017; it contains albumen and granular casts. The flow is small; 300-500 c.c. per diem as a rule. There is no retinitis.

Course. The breathing remained unaltered till death. She was often delirious at night and developed occasional incontinence. Thirst was complained of a good deal. The œdema increased and a pleural effusion developed rather rapidly. She became progressively weaker and succumbed on June the 11th. The temperature was subnormal throughout.

Post mortem. June, 1913.

The lower limbs are œdematous; the right pleura contains a pint of clear fluid; an excess of fluid is found in the pericardial and peritoneal cavities. The left pleura is obliterated by soft adhesions. The *lungs* are œdematous; there is little congestion or œdema of them. The *heart* and vessels weigh 495 grammes (muscle of R.V. 79·5; of L.V. 169·5; and of the septum 49·5 grammes). The chambers are dilated, the muscle pale and soft.

The valves are normal with the exception of the aortic segments, which though a little calcareous at their bases, are competent. The coronary orifices are open, the vessels are tortuous, dilated and atheromatous. The muscle fibres showed patchy fatty degeneration.*

The *aorta* and larger vessels show numerous patches of atheroma. The *kidneys* weigh 326 grammes ; the capsules are a little adherent ; the surfaces finely granular. The cortices are a little narrow. Under the microscope the vessels are full, the vessel walls show medial thickening. There is a good deal of scattered fibrosis, especially in the cortex ; a few of the Malpighian corpuscles are hyaline. The tubules are often isolated by fibrous tissue ; the epithelium shows disintegration.

CASE 3. (*Acidosis and C.-S. breathing.*)

A case exhibiting red granular kidneys and signs of cardiac failure. Cheyne-Stokes breathing, respiratory distress and attacks of nocturnal dyspnœa were present. Cyanosis was but slight. Special blood examinations were made on the day of death ; acidosis was found. The acidosis accounted for the respiratory distress in the absence of cyanosis. The blood contained an excess of hydroxy-acids and urea. Death occurred with signs of cardiac and renal failure.

G. C. S., a man of 67 years, was admitted to Lambeth Infirmary on January the 22nd, 1913.

History (22.1.13). He remembers no past illness and attributes his condition to a fall in December, 1910. From that time he has experienced pain in the head and between the shoulders. Shortness of breath has been present for six months ; it is increased by exertion, and he often wakes in the night in suffocative attacks which last for some while. He frequently has attacks of giddiness.

Condition (28.4.13). A wasted subject who sits in bed. The *taces* are dark, the edges of the lips are slightly cyanosed ; cyanosis is a little deeper in the ears, tongue and fingers. The *breathing* is gasping and is heard all over a large ward ; in depth it waxes and wanes periodically, often vanishing entirely. The distress is very great and during the hyperpnœic periods he is very restive. But, curiously, he states that he is better while up and about the ward. The breathing in the hyperpnœic stage is irregular.

Analysis of respiratory curve.

	HYPERPNŒA.		HYPOPNŒA.	
	DURATION.	RATE.	DURATION.	RATE.
28.4.13	50 secs.	46 p.m.	5-16 secs.	0-34 p.m.

The *heart* is enlarged (the apex is in the nipple line in the 4th space ; dulness from mid-line 2 and 5 inches). There is a general heave over the left precordium and slight thrust in the epigastrium. Systolic murmurs are heard at the apex and aortic cartilages. Fibrillation of the auricles is always present, the ventricular rate being from 110-120 per minute. *Arterial system.* The pulse is continuously grossly irregular ; the most forcible beats are obliterated by an armlet pressure of 160 mm. Hg., the less forcible beats at 150 mm. Hg.. The arteries are thickened. *Venous reservoirs, &c.* The veins are full and pulsate forcibly. The liver is much enlarged and is pulsatile. Dropsy is present in the feet and over the sacrum. There are signs of some ascites. The *kidneys.* The urine is acid, contains albumen, pus cells and granular casts ; sp. gr., 1,020. *Lungs.* There are signs of small pleural effusions, and general bronchitis.

Course. During the patient's stay in hospital his condition was almost unchanged. At nights he was often delirious. He died without further warning during the evening after the special examinations were made (28.4.13). The temperature was subnormal throughout the illness, reaching 98·6° on four occasions only.

Post mortem (30.4.13).

Slight dropsy is present in the legs and over the sacrum. There is considerable ascites, but no excess of pericardial fluid. The *lungs* are congested and show collapse ; scarrings and adhesions are present at the apices. More than a pint of fluid is found in each pleura. The *heart* and *vessels* weigh 650 grammes (muscle of R.V. 81·0, of the L.V. 187·5, and of the septum 36·5 grammes). The auricles and ventricles are dilated. The coronary vessels show a little atheroma. The valves are normal with the exception of some widening of the tricuspid orifice. The *aorta* is

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* One of two hearts examined for fat.

atheromatous throughout its whole length and small calcareous plaques are present in the abdominal aorta. The *kidneys* weigh 270 grammes. The capsules are very adherent, the surfaces red and coarsely granular, presenting many small retention cysts. The cortices are narrow. Considerable fibrosis and lymphocytosis are seen under the microscope. The Malpighian corpuscles are mostly hyaline. The epithelium of the tubules is extensively disintegrated; the vessels are thickened in the intimal coats. The *liver* shows congestion. The *brain* is normal; the pia arachnoid is opaque and œdematous.

CASE 4.   (*Acidosis with C.-S. breathing.*)

A case of cardiac failure with signs of renal involvement. Dyspnœa, associated with attacks of nocturnal distress and Cheyne-Stokes breathing, was prominent. High blood pressure was present. There was no trace of cyanosis. Special examinations explained the breathlessness; acidosis was found.

D., a jeweller of 57 years, was seen on May the 8th, 1913, for breathlessness and drowsiness.

History (8.5.13). There is no history of previous illness. For twelve months he has been short of breath with effort and upon exposure to cold. Pain in the epigastrium is also experienced. In November, 1912, the symptoms were more severe, and he was wakened at night with aggravated breathlessness. In January he had to take to bed, and seen at that time Cheyne-Stokes breathing and alternation of the heart were discovered. He improved and began to get about but has now had a relapse. To-day he has developed a severe frontal headache, has become more breathless and notices weakness and numbness in the left arm. Nocturnal micturition has been present on rare occasions.

Condition (8.5.13). The patient lies flat in bed; he is drowsy. He has absolutely not a trace of cyanosis. The *breathing* is gasping (36 per minute) and a little periodic in amplitude. He is restive.

Analysis of respiratory curves.

	HYPERPNŒA.		HYPOPNŒA.	
	DURATION.	RATE.	DURATION.	RATE.
10.5.13 ..	35 secs.	40 p.m.	10 secs.	0 p.m.
13.5.13 ..	31 secs.	24-30 ,,	31 secs.	21-28 ,,
18.5.13 ..	30-40 secs.	30-32 ,,	30-40 secs.	26-29 ,,
19.5.13 ..	30-35 secs.	42 ,,	10-15 secs.	0 ,,

The *heart* is a little enlarged. There are no murmurs. The rate is 92 per minute; the action is irregular. The a-c interval is prolonged, extrasystoles are present. *Arterial system.* There seems to be no thickening. The blood pressure varies between 200 and 210 mm. Hg. Alternation of the pulse follows the extrasystoles. The *veins* of the neck are swollen and pulsate freely. The liver is not enlarged; there is no dropsy. The *kidneys*. He passes from 650-2,000 c.c. of urine a day; it contains albumen and abundant granular casts. The retinæ are normal. The *lungs*. A few rhonchi are heard over the chest.

Course. He remained in practically the same state until May the 14th, often exhibiting Cheyne-Stokes breathing, and sleeping badly. Between the 14th and 17th there was considerable improvement, but on this day he became more drowsy towards evening, developed aphasia and left hemiplegia. On the 18th he was better, recognising people and talking a little. The jerks were increased on the right side, decreased on the left; plantar response (right and left) extensor. Improvement was considerable up to the 28th when he was last seen. The breathing was then easier (28 per minute) and fairly regular. Cheyne-Stokes breathing being but rarely in evidence. The paralysis in the left limbs is clearing up slowly; extensor response is still found in the left foot. He has travelled to Canada and died there recently.

CASE 5.   (*Acidosis and C.-S. breathing.*)

A case of cardiac and renal disease in which continuous dyspnœa, Cheyne-Stokes breathing, and attacks of intense dyspnœa (often at night) were prominent, but in which cyanosis was never great. Special blood examinations accounted for the breathlessness; acidosis was found. Death occurred with signs of circulatory failure.

F. C., a French-polisher of 53 years, was admitted to University College Hospital on January the 19th, 1913, complaining of persistent breathlessness.

History (19.1.13). With the exception of a severe bronchitic attack 10 years before, he gives no history of other illness though he had a similar seizure to the present one six years ago. His habit has been to drink two pints of beer a day. For two years there has been progressive

loss of flesh (2 stone). Shortness of breath has been continuous for three months ; it is noticed especially upon exertion ; he says that he wakes frequently at night with a feeling " as though he is drowning " ; the struggle with his breath lasts ten to twenty minutes and he goes to sleep again, often to re-awaken in the same state. Sometimes the same attacks come on by day. Headaches are experienced not infrequently.

Condition (19.1.13). An emaciated and pale subject (red cells 3,780,000 ; whites 14,750 ; neutrophile polymorphonuclear 80%,). who lies propped up in bed or sits ; there is but very slight cyanosis ; his skin is a lemon yellow colour. He is drowsy. The breathing is laboured and irregular ; it is also periodic, waxing and waning and demonstrating periods of very shallow respiration or apnœa (Fig. 7). He is restive, and the restiveness is most conspicuous during the hyperpnœic stage. He is unable to hold the breath at all, and deep breathing is followed by no abatement in the respiratory excursion.
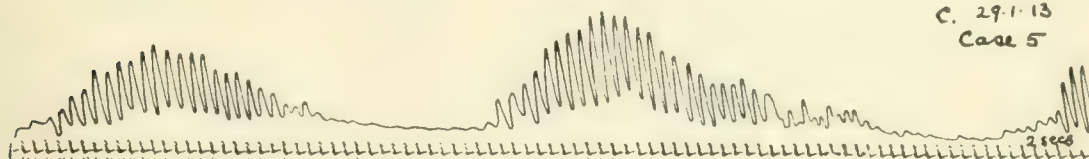
c. 29.1.13
Case 5

Fig. 7.

	HYPERPNŒA.		HYPOPNŒA.	
	DURATION.	RATE.	DURATION.	RATE.
29.1.13 ..	35 secs.	33 p.m.	15-30 secs.	0-24-20 p.m.

The *heart* is enlarged (impulse diffuse, limits of dulness from mid-line 0 and 5 inches). The sounds are normal, there are no murmurs. The mechanism is normal (electrocardiograms, &c.). The rate is excessive, lying usually near 100 per minute and being faster towards evening as a rule. *Arterial system.* The beats are equal in strength but feeble. The arterial walls seem thickened. Blood pressure 180-150 mm. Hg.. *Venous reservoirs.* There is no excess of venous pulsation or filling ; the liver margin can be felt between umbilicus and rib margin. The spleen is palpable. He has slight œdema of both ankles. *Kidneys.* The urine varies in quantity between 450 and 1,500 c.c. per diem. It is acid ; sp. gr. 1,014-32 ; a trace or cloud of albumen is present. No casts are to be found. *Lungs.* At the bases are a number of rhonchi and crepitations. *Nervous system.* Normal except for drowsiness and irritability.

Course. By the 23rd the œdema had cleared ; on the 4th he retched, and brought up a little clear fluid ; this symptom was often repeated subsequently. He slept very badly, being often disturbed by attacks of breathlessness. On the 10th of February, he developed a systolic apical murmur, and on the 17th the ankles were œdematous again. The attacks of nocturnal dyspnœa increased in frequency and severity towards the end of this month, as did also the œdema. On the 3rd March signs of a commencing effusion were noticed at the right base. On the 5th he had several severe attacks of dyspnœa towards evening, accompanied by very frequent and gasping respirations (rate 40-50 per minute) ; these periods lasted a minute and tended to recur after short intervals. Towards the end of each period of hyperpnœa, restlessness was very great and he complained of pain of anginal distribution. This subsided as the hyperpnœa lessened. The complete period of great distress lasted for several hours and was repeated each afternoon for many days ; it was accompanied by profuse sweating and followed by exhaustion and dread of its recurrence. By the 7th of March dropsy had increased and about this time the usual periodicity of the breathing vanished, and was replaced by irregular laboured breathing, Cyanosis though never prominent increased a little. On the 17th he had a fit in the night, beginning with twitching in the limbs and ending in unconsciousness lasting for a half hour and being succeeded by a long period of drowsiness. On the 28th, the legs were drained. Next day a similar fit, with unconsciousness of 40 minutes duration, occurred. On the 1st of April he coughed up blood-stained sputum. On the 7th sepsis developed in the left leg and from this time he became progressively weaker ; he died from general exhaustion on the 26th. Up till the time when the leg became septic the temperature was almost always subnormal, reaching 99 on one occasion only.

Post mortem. (27.1.13.)

A sallow, wasted body (weight 7½ stone. Considerable dropsy is present in the legs and an excess of fluid in the pericardium. The lungs are emphysematous and œdematous ; in the right are large thrombotic infarcts. The right pleura contains two pints of fluid and the pleura is covered with recent blood-stained lymph. The left pleura contains a pint of clear fluid. The *heart*. The heart and vessels weigh 425 grammes (muscle of R.V. 90·5, of L.V. 175·5, and of septum 42·5 grammes). The chambers are dilated and the muscle friable. Ante-mortem clots are found in the left ventricular apex. The coronary arteries are tortuous and very calcareous. With the exception of dilatation of the tricuspid ring the valves are normal. The *aorta* and large vessels show a mild grade of atheroma. The *kidneys* weigh 400 grammes ; the capsules are very thick, strip with difficulty and leave finely granular torn surfaces. The pelves are wide, the actual kidney substance seeming to be reduced. Microscopically examined the organs are engorged, show a good deal of interstitial fibrosis and patchy collections of lymphocytes ; the tubules are distended, the epithelium being flattened and disintegrated. The Malpighian corpuscles are congested. The vessels show medial thickening. The *liver* and *spleen* are large and congested, the former showing fibroid and fatty change also.

CASE 6. (*Acidosis and C.-S. breathing.*)

A case of rheumatic heart disease, exhibiting persistent paroxysmal tachycardia, heart block, aortic regurgitation and angina pectoris. Dyspnœa, accompanied by Cheyne-Stokes breathing, was a prominent symptom. High blood pressure was usually present. Cyanosis was never a prominent symptom. Special blood examinations fully explained the dyspnœa and revealed a condition of acidosis. There were signs of some renal involvement.

A. S., a man of 57 years, was admitted to University College Hospital on May the 9th, 1911, complaining of breathlessness and swelling of the feet.

History (9.5.13). A daughter is under treatment for mitral stenosis of rheumatic origin. He acquired rheumatic fever at 26 years of age. His first symptom of his present complaint appeared in May, 1911, in the form of shortness of breath and swelling of the feet. He suffers from giddiness and attacks of pain in the left side of the chest and arm. The latter becomes numb. The attacks are accompanied by choking sensations in the throat. He has been under observation in a very similar condition for two years, spending the greater part of his time as an inmate of various hospitals. He improves during hospital treatment but reverts to his original condition within a short time of his discharge.

Condition (19.5.13). The patient is a heavy-framed, though rather wasted subject, who suffers from orthopnœa. The *face* is sallow, and he has distinct cyanosis of the lips, but none of the ears and cheeks. The *breathing* is quickened but not distressed while he rests. It is periodic, waxing and waning, and often progressing to apnœa of short duration (see Fig. 8). The *heart* is enlarged (limits of dulness, 2 and 5¼ inches from the mid-line ; apex diffuse). To and fro aortic murmurs are heard and a blowing systolic murmur at the apex. The 2nd aortic sound is not audible. He has a condition of persistent paroxysmal tachycardia ;* short paroxysms succeed each other rapidly (Fig. 9). Electrocardiographic examination shows that they arise in a new auricular focus. The *P-R* interval is always long and occasionally beats are missed. The rate of the heart when it beats naturally is 60-80 ; during the paroxysms its rate is 120-160. *Arterial system*. The pulse is full and water-hammer in character ; capillary pulsation is present. The blood pressure varies from 150-200 mm. Hg.. The arteries are tortuous and thickened. *Venous reservoirs, &c.* The veins are very prominent and pulsate with almost arterial force. The liver is enlarged and pulsatile. He has dropsy of the feet. The *kidneys*. The urine varies from 1,100-2,500 c.c. per diem ; sp. gr. 1.015 ; a trace or cloud of albumen is found ; granular casts are present. The retinæ are normal. The *lungs*. The percussion note is impaired at the bases.

Course. The periodic breathing was persistent ; he often experienced exaggerated breathlessness at night. Dryness of the mouth and thirst were complained of. The temperature was subnormal on almost all occasions. During his stay his symptoms were but little relieved.

On May the 26th, his respiratory ventilation was measured. He filled a 160 litre gas bag in 12 mins. 18 secs., and in 11 mins. 20 secs. The output averaged 13·5 litres per minute. The output per respiration, counting the breaths on respiratory curves during each observation, came to 429 c.c. per respiration (number of respirations 396 on each occasion).

CASE 7. (*Acidosis and C.-S. breathing.*)

A case of cardiac, arterial and renal disease. High blood pressure, continuous dyspnœa, accompanied by Cheyne-Stokes breathing, and without undue cyanosis, were features of the case. Special blood examinations explained the respiratory distress ; acidosis was found. Death occurred with signs of cardiac failure.

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* These have always been present, see Agassiz' report, Heart, 1911-12, III, 193.
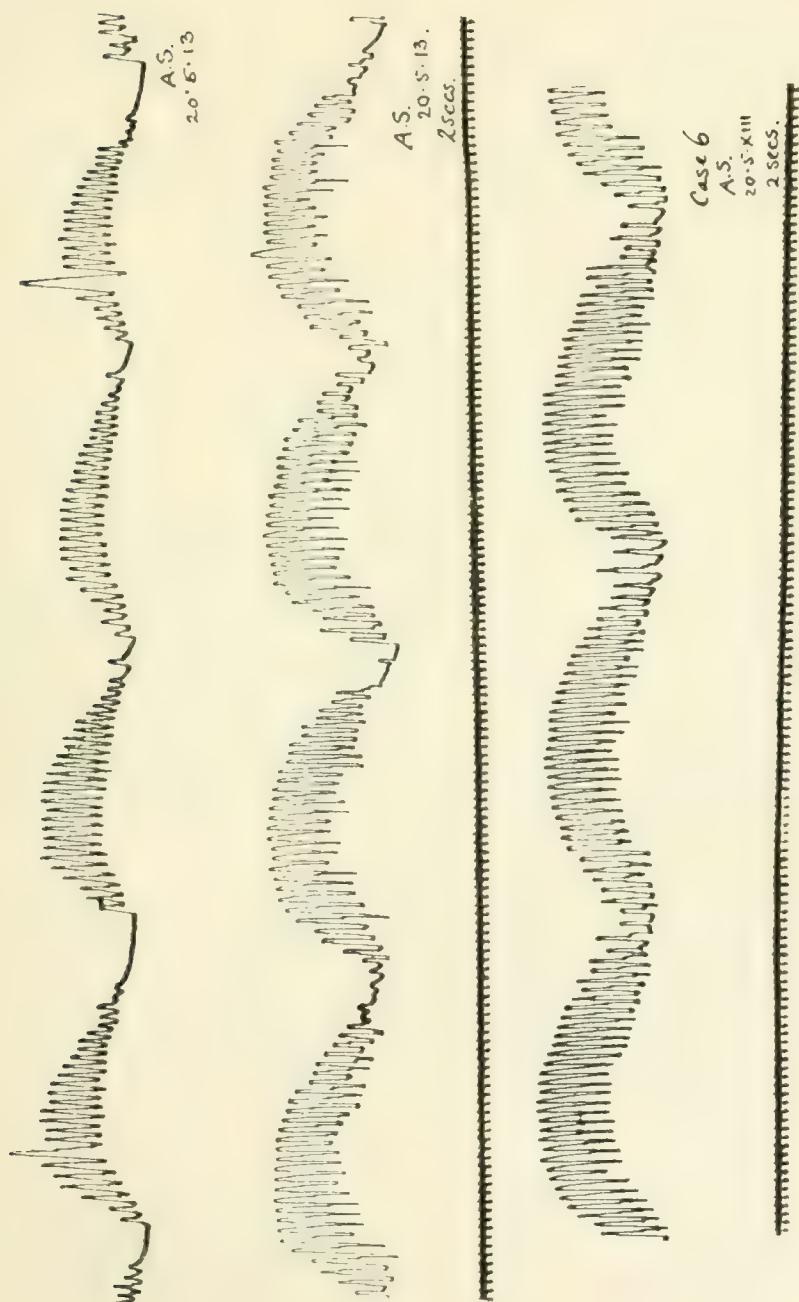
Fig. 8.

F. J. S., a man of 63 years, was admitted to Lambeth Infirmary, complaining of breathlessness and swelling of the legs.

History (14.5.13). There is no history of past illness. He has been ailing for nine months, shortness of breath upon exertion being the chief symptom. Over the same period he has experienced sensations of choking at night ; he wakes frequently to find himself very breathless. The intensified attack may last a few minutes or half an hour or more. He has been accustomed to micturate several times at night. Swelling of the feet commenced a month ago.

Condition (14.5.13). A wasted man who sits propped in bed with pillows ; the complexion is pigmented and his expression anxious. He has slight cyanosis of lips, ears and fingers. The breathing is distressed and periodic, waxing and waning to regular periods of apnœa (Fig. 10). He is restive during the hyperpnœic phases. Slight exertion increases his distress and he is unable to hold his breath during the period of breathing.

Analysis of respiratory curves.

	HYPERPNŒA.		HYPOPNŒA.	
	DURATION.	RATE.	DURATION.	RATE.
9.5.13 ..	27 secs.	39 p.m.	9-11 secs.	0-39 p.m.
19.5.13 ..	30-35	42 p.m.	10-15 secs.	0

The *heart* is enlarged (impulse in the 4th and 5th spaces ; limits of dulness 1 and 6 inches from the mid-line). There is no sign of valve lesion ; gallop rhythm is heard at the apex. The mechanism is normal. The heart rate varies between 90-120 ; it is usually over 100, and faster at night. *Arterial system.* The pulse is feeble, the blood pressure varies between 200 and 220 mm. Hg.. The arteries are very tortuous and thickened. *Venous reservoirs, &c.* The veins are a little prominent and pulsate vigorously. The liver is felt as low as the umbilicus and pulsates. He has œdema of the legs and back. The *kidneys.* The quantity of urine is usually less than normal ; it is of high colour, and contains albumen and granular casts ; sp. gr. 1,017. *Lungs.* There are signs of a pleural effusion on the right side.

Course. The breathing remained unaltered until the end. On the 7th of May three pints of fluid were drawn from the right pleura ; four pints of fluid were also taken away on the 27th and on the 5th of June. Cyanosis was never conspicuous. He became progressively weaker and the dropsy increased. Thirst was a prominent symptom. He died on June the 14th. The temperature was subnormal throughout his illness.

Post mortem. (15.6.13.)

There is general anasarca ; the right pleura contains three pints of clotted fluid, the left about a half pint. The right lung is compressed, the left congested. The *heart* and vessels weigh 626 grammes (muscle of R.V. 88·5 ; of L.V. 123·0 ; and of septum 73·5 grammes). The cavities are dilated. The muscle showed advanced fatty degeneration.* The valves, with the exception of widening of the tricuspid ring, are normal. The coronary openings are normal, the vessels are open but stiff with atheroma and calcareous deposit. The valves are normal with the exception of some widening of the tricuspid ring. The *kidneys* weigh 270 grammes. The capsules strip easily, leaving finely granular surfaces. The cortices are not reduced. Under the microscope the vessels are engorged, and show medial thickening. There is considerable diffuse fibrosis. The Malpighian corpuscles are engorged but otherwise normal. The epithelium of the tubules shows little change.

The *liver* is enlarged and congested.

CASE 8. (*Acidosis and C.-S. breathing.*)

A case exhibiting arterio-sclerosis and fibrosis of the kidneys with signs of cardiac degeneration. High blood pressure, Cheyne-Stokes breathing and distressed breathing were conspicuous features of the condition ; cyanosis was slight. Special blood examinations showed a condition of acidosis which accounted for the dyspnœa. Death occurred with signs of cardiac failure.

J. S., a man of 64 years, was admitted to Lambeth Infirmary on February the 21st, 1913, complaining of shortness of breath.

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* One of two hearts examined for fat.

1/5 sec.

Case 6

A S.
18·5·13

Fig. 9.

J.J.S.
9·5·13

Case 7

2 secs
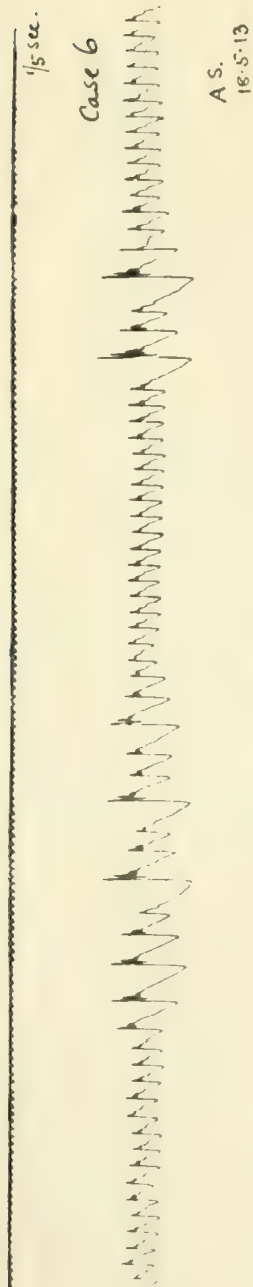
Fig. 10.

Fig. 10.

History (21.2.13). The past history throws no light upon his illness. It is said that breathlessness has been present for six weeks, and has been so severe as to confine him to bed for a fortnight.

Condition (7.3.13). The patient is pallid, he is but slightly cyanosed ; he sits propped up in bed with pillows. The *breathing* is laboured, noisy and accompanied by considerable distress. The amplitude of respiration waxes and wanes periodically, ending in long apnœic periods. During the hyperpnœic stage the breathing is regular, but he is very restive. He is *delirious* and very drowsy.

The *heart* is enlarged (impulse in 4th and 5th spaces outside the nipple ; limits of dulness 1¼ and 5 inches and in the 3rd space). A good deal of shock is felt over the precordium. There is no sign of valvular disease ; gallop rhythm is heard at the apex. The mechanism of the heart is normal ; the rate usually lies between 72 and 100 per minute. *Arterial system.* The pulse wave is feeble, but the blood pressure is high (190-200 mm. Hg.). The vessels are thickened. *Venous reservoirs.* The veins are full. The liver and spleen are palpable ; much œdema of the hands, feet and back is present. *Kidneys.* The urine contains albumen. *Lungs.* The percussion note is impaired at both bases and the breath sounds are weak.

Course. The patient continued in the same state until the 23rd, when death supervened. The temperature was subnormal throughout ; average 97·5° Fahr..

Post mortem. (24.3.13.)

The trunk and limbs are dropsical ; an excess of fluid is found in the pericardial and peritoneal cavities. The lungs are emphysematous and the lower lobes congested. Each pleura contains over a pint of fluid. The *heart* and vessels weigh 695 grammes (muscle of R.V. 104·0, of the L.V. 191·0, and of the septum 61·2 grammes). There are no adhesions. The cavities are dilated. The coronary vessels are dilated and rigid. The valves are normal. The *aorta* and large vessels show general athero-sclerosis. The *kidneys.* The right organ is small and coarsely granular, presenting many large retention cysts. The capsules are adherent and the cortex very thin. Under the microscope profound interstitial changes are seen, fibrosis being greatly in evidence, and many of the Malpighian corpuscles being hyaline. The tubules are largely denuded of epithelium. The vessels show medial and internal thickening. The left organ is enlarged, the surface finely granular, the cortex diminished in size. Scattered collections of lymphocytes are seen ; there is a good deal of fibrosis ; the vessels show great intimal thickening ; the tubules are distended and the epithelium is ragged. The *liver* and *spleen* are large, congested and friable.

CASE 9. (*Acidosis without C.-S. breathing.*)

A case of cardiac failure with some signs of renal involvement, in which dyspnœa, accompanied by but very slight cyanosis, was prominent. Special examinations completely explained the dyspnœa and proved the presence of acidosis. After a few weeks stay in hospital the dyspnœa subsided and the acidosis disappeared.

M. P., a married woman of 61 years, was admitted to the City of London Hospital complaining of breathlessness.

History (21.5.13). She had measles and scarlet fever as a child. For 12 years she has been the subject of a winter cough. For two months she has been short of breath ; it is felt most in the early morning, when the weather is cold and upon exertion. Palpitation, cough and pain in the left chest have been present for the same period. She is losing flesh. For a week slight swelling of the feet has been noticed.

Condition (23.5.13). A poorly nourished woman (weight 8 stone 2 lbs.), she sits in bed. There is very slight cyanosis of the edges of the lips and of the tongue ; the cheeks and ears are of normal colour. The *breathing* is hurried (30-40 per minute) ; it is irregular, and there is some distress. After taking twelve deep breaths a pause of three seconds occurs ; three small respirations are then taken, a pause and a further group of three respirations follows. Then there is a pause and the respirations which follow show a slight staircase until her natural respirations are resumed (Fig. 11). She can hold her breath for no more than four seconds. Cheyne-Stokes breathing has not been seen, she has been closely watched for it. The *heart* is enlarged (impulse diffuse in 5th and 6th spaces ; limits of dulness 1¼ and 5¼ inches from mid-line). There are no murmurs ; gallop rhythm is present at the apex. The heart rate varies from 80 to 100 ; occasional extrasystoles interrupt its otherwise regular action. *Arterial system.* The arteries are thickened, the blood pressure varies from 170 to 200 mm. Hg.. There is no alternation. The *veins* seem normal ; the liver is slightly enlarged. Slight dropsy of the ankles is present. The *kidneys.* The urine is increased in quantity ; a trace of albumen is present. There are no casts. The retinæ are normal. *Lungs.* A few crepitations are heard at the bases.

↓ Forced Breathing ↓   Case 9

M.P.
23·5·13.
2 secs
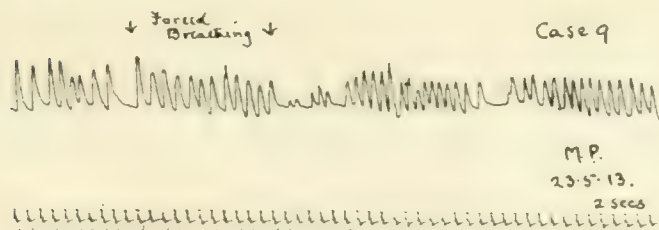
Fig. 11.

Course. During the five weeks' stay in hospital, her condition gradually improved until she lost her breathlessness, and was able to walk about without discomfort. At no time was Cheyne-Stokes breathing observed. During her stay there were several attacks of nocturnal dyspnœa, one of which lasted 20 minutes. She suffered a good deal from thirst. Her temperature was almost always subnormal.

CASE 10. (Acidosis without C.-S. breathing.)

A case of cardiac failure, with some signs of renal involvement, in which dyspnœa, in the absence of what could be considered an equivalent grade of cyanosis, was a prominent symptom. Cheyne-Stokes breathing was never observed. Special examinations explained the dyspnœa and revealed acidosis.

H. P., a window cleaner of 50 years of age, was admitted to University College Hospital on the 14th April, 1913, complaining of shortness of breath, giddiness and cough.

History (14.4.13). He has had no illness except typhoid fever 29 years ago. For 20 years he has had attacks of breathlessness accompanied by pain in the chest and giddiness. The attacks are induced by effort and they last many weeks. In recent attacks the left arm has swollen and he has experienced nocturnal breathlessness. He wakes repeatedly in the night to find his breath short.

Condition (15.4.13, &c.). The patient is orthopnœic ; he has slight cyanosis of the lips ; the cheeks and ears are more deeply cyanosed. The *breathing* is hurried (34-40 per minute) but regular. There is no reserve. The *heart* is enlarged (impulse not felt ; limits of dulness 1 and 5 inches from mid-line). There are no murmurs ; gallop rhythm is heard at the apex. The mechanism is normal. The rate varies between 84 and 125 ; usually it lies near 100. *Arteries.* The pulse is regular and shows no alternation. The vessel walls are thickened. The blood pressure varies around 180 mm. Hg. (sometimes it reached 200 mm.). *Venous system.* The venous pressure is raised. He has evident signs of obstruction to the superior vena cava (this is of 16 years standing). The liver is a little enlarged. The *kidneys.* The urine flow varies between 350 and 1,100 c.c. per diem ; sp. gr., 1,010-20. The urine contains a little albumen, and granular casts. The retinæ are normal. *Lungs.* There are no signs.

Course. From his admission to the time when the special examinations were made, there was no perceptible change in his condition ; the temperature was almost always subnormal.

CASE 11. (Acidosis without C.-S. breathing.)

A case of rheumatic heart disease (mitral stenosis) admitted for cardiac failure (auricular fibrillation). She developed a very rapid heart action and died during the attack. Breathlessness was urgent, and the patient considerably cyanosed. A special blood examination was made during the attack and acidosis was found. The condition shortly ended fatally.

C. S., a woman of 54 years, was admitted to University College Hospital complaining of breathlessness and swelling of the legs on April the 22nd, 1913.

History (22.4.13). At 22 she suffered from rheumatic fever and has been laid up on three occasions since with the same complaint. Shortness of breath, intensified by exertion, and palpitation have been present for four years. Swelling of the legs and abdomen first developed two and a half years ago.

Condition (22.4.13). A thin, sallow woman, who sits in bed. There is a good deal of cyanosis of the lips, cheeks, ears and hands. The *breathing* is very laboured and rapid ; there is absolutely no reserve. The *heart* is enlarged, and there are evidences of mitral regurgitation and stenosis. Auricular fibrillation is present, the ventricular rate being 140 per minute. *Arterial system.* The pulse is grossly and continuously irregular, the arteries are thickened. *Venous resources, &c.* The veins are very prominent and pulsate forcibly ; the liver is enlarged and pulsates ; dropsy of the legs and sacrum are present ; she has a very large ascitic collection. *Kidneys.* The

urine is of high colour and sp. gr. ; small in quantity and contains albumen. *Lungs.* General bronchitic signs are heard over the thorax ; and there are signs of pleural effusions at both bases.

Course. The patient developed a sudden attack of regular tachycardia on the 27th, the heart rate rising to 180-200 per minute. The cyanosis increased, and the respirations became still more laboured but maintained their regularity (rate 38 per minute) The blood was examined during the attack, from which she failed to recover. Death occurred on the 30th of April.

Post mortem. (1.5.13.)

General dropsy, effusions into both pleural cavities and much ascites, are present. The *lungs* are œdematous and congested. The *heart* and vessels weigh 460 grammes (muscle of R.V. 98·5 ; of L.V. 158, and of septum 35·5 grammes). The aortic valves are thickened and incompetent through an orifice of 16 sq. mm. ; the mitral orifice is stenosed (orifice 220 sq. mm.) ; the tricuspid ring is dilated. Minute vegetations are found on the pulmonary valve. The left auricle is greatly dilated and hypertrophied. The *aorta* and large vessels are atheromatous. The *kidneys* weigh 255 grammes ; the capsules strip leaving finely granular surfaces. The cortices are perhaps a trifle narrow ; in several places they are deeply scarred. Microscopically the kidneys show little change apart from congestion, and fibrosis at the points of scarring. The *liver* and *spleen* are congested.

CASE 12. (*Special control.*)

A case of high blood pressure, with signs of arterial disease, enlargement of the heart and liver and some signs of renal involvement. He was examined, while convalescent from an attack of hæmoptysis and dyspnœa in which Cheyne Stokes breathing appeared, as a special control.

J. J., a man of 56 years, was admitted to University College Hospital on May the 13th, 1913. Two days before he became suddenly dyspnœic, coughed and spat up blood. Since, he has had palpitation, and breathlessness with slight exertion. Apart from " influenza " many years ago he gives no history of former illness. He has smoked excessively, but has taken alcohol in moderation.

Condition (13.5.13). A thick-set plethoric subject, he is a little cyanosed and orthopnœic and has well-defined Cheyne-Stokes breathing ; the respiratory rate during the hyperpnœic period is 32. The *heart* is enlarged (limits from mid-line 1½ and 5½ inches). Systolic murmurs are heard at the apex and over the aortic cartilage. The shock is a little increased over the left side of the precordium. The heart's mechanism is normal ; rate 88 per minute (electrocardiograms). *Arterial system.* The pulse is full, the blood pressure 180-200 mm. Hg., The arteries are tortuous and thickened. The *venous reservoirs, &c.* The veins are full and pulsate freely ; the liver, the edge of which is hard, is felt a little above the umbilicus. The *kidneys.* The urine flow is from 900-2,750 c.c. per diem ; it contains albumen, granular and epithelial casts. He has no retinitis. The *lungs.* Rhonchi are present over the whole chest.

Course. On admission he was bled freely and purged. The breathing lost its periodicity on the 16th, and respiration became much freer. Some cyanosis remained in lips and tongue on the 18th. By the 26th the respiration was almost natural, being almost quite regular at 19 per minute. On this day some reserve was shown ; the breath could be held for 18 seconds without discomfort and deep breathing was followed by a period of apnœa ; but even at such times no periodicity was observed. He was discharged from hospital on this day.

CASE 13. (*Cardiac dyspnœa.*)

A case of cardiac and arterial disease, with some signs of renal involvement, admitted with symptoms of circulatory failure and respiratory embarrassment. Special examinations were made during the convalescent period and when the breathing was free while the patient rested. No undue acidosis was found ; the absence of respiratory reserve was attributable to accumulation of CO resulting from the circulatory condition.

T. C., a manservant of 49 years, was admitted to University College Hospital on January the 31st, 1913, with signs of cardiac failure.

History (31.1.13). The past history speaks only of numerous attacks of " influenza." He has suffered from heart disease for four years and has been under observation for two years. Breathlessness has been the prominent symptom throughout ; it is always present in some degree while he is up and about, and from time to time becomes aggravated and is associated with palpitation, blueness and swelling of the feet. He is a sufferer from chronic bronchitis and emphysema.

Condition (31.1.13). A spare subject, who is very cyanosed and orthopnœic. The chest is barrel shaped and rather rigid. The *breathing* is laboured and rapid and somewhat irregular. The *heart* is enlarged (limits of dulness from mid-line 1 inch and 4½ inches) ; there are no murmurs.

He exhibits paroxysms of tachycardia (which electrocardiograms show to originate in a new auricular focus) ; during the paroxysms the rate is 160 ; while the mechanism is normal, the rate is 90, and alternation is often discovered after extrasystoles. *Arterial system.* The pulse is feeble ; the blood pressure varies between 150 and 130 mm. Hg.. The arterial walls are thickened. *Venous reservoirs.* The veins are very full and pulsate forcibly ; the liver is enlarged and pulsatile. Dropsy is present in the feet. *Kidneys.* The urine varies in quantity, being usually about 1,000 c.c. a day and on one occasion reaching 3,600 c.c.. A trace of albumen is present from time to time. The retinæ are normal. *Lungs.* There are signs of generalised bronchitis and emphysema.

Course. During a stay of fourteen weeks his improvement was slow, but at the time special examinations were made (21.4.13), he was convalescent. His condition at that time may be judged from the tables. Cheyne-Stokes breathing was never seen. The most important incident of his illness was a series of fits of brief duration, and occurring on March the 13th and 14th. These were accompanied by loss of consciousness and a rise of blood pressure to 180 mm. Hg..

CASE 14. *(Cardiac dyspnœa.)*

A case of choreic heart disease (mitral stenosis, &c.), admitted with signs of grave circulatory failure and respiratory embarrassment. Special examinations were made when the patient had improved a little, but while the signs of failure were still prominent ; no undue acidosis was found ; the dyspnœa was attributable to accumulation of CO_2 resulting from the circulatory condition.

E. M., a married woman of 29 years, was admitted to University College Hospital, suffering from old standing symptoms of cardiac failure.

History (April, 1913). She had St. Vitus' dance at the age of 6 years. At 18 she easily became short of breath when exerting herself and about the same time the legs and abdomen became swollen. These symptoms have been present, sometimes more and sometimes less, ever since. She has been in hospital on several occasions. The present aggravation of the symptoms is of 14 days duration ; blood-stained sputum and vomiting have been present.

Condition (April, 1913). The patient is orthopnœic and the skin is urobilin stained. Cyanosis is very deep. The *breathing* is very laboured, rapid and irregular. The *heart* is greatly enlarged (limits of dulness 2 and 7 inches from the mid-line). There are evident signs of mitral stenosis, with fibrillation of the auricles and an irregular ventricular action at 120-140 per minute. The *arterial system.* The arteries seem normal ; the pulse is continuously irregular and feeble ; the blood pressure (most forcible beats) varies between 90 and 100 mm. Hg.. *Venous reservoirs.* The veins are fully distended and pulsate forcibly. The liver has swollen below the umbilicus, and pulsates. *Kidneys.* The urine flow is reduced ; the urine is of high colour (sp. gr. 1,026-38), and contains albumen and a little blood. Casts are not found. *Lungs.* Crepitations are heard all over the chest.

Course. The patient was treated upon digitalis and had improved to some extent when the special observations were made. Her condition at this time may be judged from the tables.

CASE 15. *(Cardiac dyspnœa.)*

A case of rheumatic heart disease, admitted with signs of circulatory failure and respiratory embarrassment. Special examinations were made during the convalescent period and when there was but little breathlessness. No undue acidosis was found.

W. C., a cardriver of 44 years, was admitted to University College Hospital in May, 1913, for symptoms of cardiac failure.

History (May, 1913). He had rheumatic fever at the age of 12 years. He has drunk immoderately but has been steady for five years. For five weeks shortness of breath on exertion, palpitation and pain in the epigastrium have been present.

Condition (May, 1913). The patient is orthopnœic and moderately cyanosed. The *breathing* is rapid and laboured. The *heart* is enlarged (limits of dulness 1 and 4½ inches from the mid-line). There is a systolic apical murmur and gallop rhythm is present. He has fibrillation of the auricles, the ventricles responding rapidly (rate 130). The *arteries* are thickened ; the systolic blood pressure (most forcible beats) varies from 160 to 190 mm. Hg.. The *veins* are engorged, the liver greatly enlarged and pulsatile ; he has some œdema of the feet. *Kidneys.* The urine-flow varies from 500-1,400 c.c. per diem ; it contains a cloud of albumen but no casts. *Lungs.* Rales and rhonchi are heard all over the whole chest.

Course. The patient was treated with digitalis and improved greatly ; the fibrillation continuing but the pulse rate falling and the signs of stasis clearing. His condition at the time of the special examinations may be judged from the tables.

CASE 16. (Control.)

H. H., a carpet salesman, aged 45, was admitted to University College Hospital on May the 29th, 1913, complaining of wasting, night sweating and feelings of nausea and sickness in the morning. At the age of 12 he had had rheumatic fever and chorea, at 20 he had suffered from sciatica and lumbago.

Condition (9.6.13). At the time of observation, as he lies in bed, he has no symptoms. His colour is high and he has slight cyanosis of the lips, cheeks, ears and fingers.* The pulse rate is 88 ; the radial and bracheal arteries are a little tortuous and show some thickening. The blood pressure is 134 mm Hg.. The heart seems normal. Respiratory rate 17 per minute ; the breathing is perfectly free. The urine is normal.

CASE 17. (Control.)

R. G., a caretaker, aged 56, was admitted to University College Hospital with symptoms of acute appendicitis on May the 24th, 1913. He was explored and a small abscess and an adherent appendix were found ; the latter was removed and the wound drained. By June the 7th, the wound had almost closed, by the 12th it had completely healed.

Condition (11.6.13). A powerfully built man. There is a very slight tinge of cyanosis of the lips, but none of the tongue, cheeks or ears ; it is no more than is seen in many apparently healthy men of this age. The heart shows no abnormality. The pulse rate is 78, respirations regular at 24 per minute and perfectly free. The urine is normal. There is a moderate grade of arterial thickening.

CASE 18.. (Control.)

Wm. S., a warehouse porter of 61 years, was admitted to University College Hospital for the treatment of a rectal fistula. His operation was upon June the 4th, 1913. The observations were made upon June the 20th, during convalescence.

Condition (20.6.13). At this time, the pulse rate was 62, the heart showed no abnormal signs. The respiration was regular and free at 16 per minute, with plenty of reserve. The arteries seem normal ; the urine is normal. Colour, a mere trace of cyanosis of the lips, but none of the cheeks, ears or fingers.

CASE 19. (Control.)

S. G., a married woman, aged 54, admitted to University College Hospital for a fracture of the patella, which was treated by wiring. She was convalescent at the time of observation.

Condition (18.6.13). Respiration free, regular, with full reserve ; rate 18 per minute. Pulse 58 per minute. Heart normal. Urine normal. The colour of the lips not unnatural for a woman of her age ; they show a little blueness (very slight cyanosis). The tongue is similarly coloured. Ears, cheeks and finger tips are of normal colour.

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* It may be remarked that certain of our simple controls are described as having slight cyanosis. It is always difficult to estimate the degree of cyanosis in a given case ; and for purposes of comparison we take as our standard the pink coloration of children ; the majority of elderly subjects exhibit, when judged by this standard, a slight amount of cyanosis.

PAROXYSMAL TACHYCARDIA AND THE EFFECT OF STIMULATION OF THE VAGUS NERVES BY PRESSURE.

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Few cases of paroxysms of tachycardia, due to impulses arising in the walls of the ventricles, have been reported. So far, only one patient suffering from prolonged paroxysms of this nature has been observed. This case was described by Lewis.[13]* Three cases exhibiting short paroxysms have been studied, two by Lewis,[10 & 13]† and one by Hart,[1] who have published electrocardiographic curves illustrating the conditions found in them. Other cases also subject to short paroxysms have been reported by Ken Kuré,[8] Lea,[9] Palfrey[15] and Pan,[16] but none of these reports is accompanied by electrocardiograms, and an exact classification of them is therefore impossible. In the present report, another instance of paroxysmal tachycardia is described and electrocardiograms shown, in which both prolonged paroxysms, and sometimes short ones, possibly of ventricular origin occurred. In any case, it differs from those already reported. In contrast to this case, one in which the origin of the paroxysms of tachycardia arose in the auricles, is described. In addition to the interest in the nature of the cardiac mechanism in each case, both afford added interest on account of the observed effects of stimulation of the vagi by pressure.

Pressure on the vagus nerves, as a method of influencing the rate of the heart, is well known and has been practised as a diagnostic and a therapeutic procedure by many observers. In the belief that paroxysmal tachycardia had a relation to the inhibitory nervous mechanism of the heart, clinicians have, in many instances, attempted to bring the attacks to an end by pressure on the vagus. Such attempts have been reported by Bensen,[1] Hay,[5] Hoffmann,[6 & 7] Ken Kuré,[8] Lewis,[11 & 12] Preisendorff,[17] Schott,[20] Weidner[21] and Wenckebach.[22] and stoppage of the paroxysms was obtained by Bensen, Hoffmann, Preisendorff, Weidner and Wenckebach. But the number of failures is apparent and has led to a general distrust of this method. Lewis[12‡] says, in fact, "Vagal excitation has also been adopted as a means of checking paroxysms of tachycardia, and met with conspicuous success in Bensen's case : but, as a general rule, it is of no avail." But distrust of the method has been due not only to its apparent failures, but to the fact that other

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* Loc. cit., p. 170 and Fig. 135.
† Loc. cit., p. 168 and Fig. 132.
‡ Loc. cit., p. 259.

measures succeeded where it failed and indicated a lack of specificity in the procedure. These other measures include enforced vomiting, compressing the abdomen, either by direct pressure or by bending at the hips, swallowing, deep breathing, psychic disturbance, &c. Most of these procedures are capable of influencing a reflex arc, the efferent limb of which starts at the cardio-inhibitory centre. The failure of vagus pressure, when one of the other measures succeeds, may be due to the fact that the one succeeds in stimulating the inhibitory mechanism, while the other fails. Most observers have reported pressing only one vagus nerve and have failed to state in most instances which one was pressed. In a few instances, both nerves were tried without success.[11]

In recent years, more detailed investigations have widened the knowledge of paroxysmal tachycardia, showing it to result from disturbances of the heart's action, multiform in nature. The attacks are now known to result from impulses originating in different portions of the heart, and the hearts subject to them do not beat under normal controlling influences. The paroxysms in a given case, with very few exceptions, present the same mechanism in all attacks, and suggest that the same abnormal factor underlies the derangement which the morbid mechanism discloses.

The association in a number of patients between certain abnormal cardiac mechanisms and defects in the inhibitory control in their hearts led one of us[2] to investigate what difference, if any, existed in the mechanism of the two vagus nerves. A similar investigation was undertaken by Robinson and Draper[18] in patients, in whom the results of pressing the two vagus nerves were compared. The results obtained by them showed distinct differences between the two nerves in some of the patients studied, but further studies have failed to show that these differences can be usually elicited. In the experiments of one of us,[3] which were carried out on dogs, simpler conditions were obtained, and then quite characteristic differences between the action of the two nerves were observed. These results were substantiated later by Robinson.[19] The action of the right vagus nerve was shown to be the one commonly accepted as that illustrating the action of the vagus nerves in general; stimulation of its peripheral stump (the left nerve being cut) stopped the whole heart. Stimulation of the left nerve (the right one being cut) slowed but did not stop the auricles and produced increased difficulty in the propagation of impulses from auricles to ventricles, so that various degrees of heart block resulted, ranging from delay in conduction to complete dissociation.

This difference in the action of the two inhibitory nerves suggested the study of patients with paroxysmal tachycardia, the defect in whom seems to lie in their inhibitory control. In some of these cases the attacks of tachycardia originate in the auricles, while in others the ventricles or the subauricular tissues seem at fault. It is natural to assume that a relation may exist between paroxysms starting in the auricles and the right vagus nerve which exerts its influence mainly on them, and between paroxysms

starting in the ventricles and the left vagus nerve, which exerts its influence mainly on the junctional tissues and on the ventricles. The two patients exhibiting paroxysmal tachycardia now reported were observed from the point of view of the conclusions arrived at in the experimental investigation.

CASE 1.

History. D. T. is an insurance agent, forty-eight years of age. His family history is good. He had malaria, measles and mumps when young, and typhoid fever at five. Nine years ago he had acute articular rheumatism, which kept him in bed two months. He had no heart involvement. He had no treatment. Three years ago he had chronic ethmoiditis. He denies having had gonorrhœa or syphilis. He has smoked excessively for many years and has occasionally been a heavy drinker.

In December, 1909, he complained of nervousness, fatigue, depression, abdominal distension and a tendency to diarrhœa, and a sense of oppression in the chest. He complained of attacks of palpitation and also of dyspnœa on exertion. The first attack of palpitation occurred in the spring of 1904, after the attack of rheumatism, but as early as December, 1899, the patient felt thumps in his chest, resembling those he feels when his attacks of palpitation terminate. After recovery from rheumatism, after exerting himself violently, he became aware of great palpitation of the heart, which ceased quite abruptly after a time. In September, 1912, the patient's general condition was worse. He was suffering from alcoholism, had a tendency to vertical headache, and complained of polyuria. He had no constipation ; his appetite was good.

The frequency and duration of the attacks may be seen from the following record :—

Date.	Duration.	Time of Day	Date.	Duration.	Time of Day.
1912 Apr. 7	50 min	P.M.	1912-13 Sept. 7	50 min.	P.M.
Apr. 9	36 ,,	P.M.	Sept. 14	55 ,,	A.M.
Apr. 22	1 hr. — ,,	P.M.	Sept. 25	1 hr. 25 ,,	A.M.
Apr. 28	5 ,,	P.M.	Oct. 1	4 ,, 10 ,,	P.M.
May 2	1 ,, — ,,	A.M.	Oct. 2	5 ,, 30 ,,	—
May 2	50 ,,	P.M.	Oct. 29	1 ,, 30 ,,	P.M.
May 8	3 ,, 50 ,,	P.M.	Nov. 8	40 ,,	P.M.
May 19	1 ,, 50 ,,	P.M.	Nov. 12	55 ,,	P.M.
June 2	40 ,,	A.M.	Nov. 15	2 ,, 3 ,,	A.M.
June 28	5 ,,	P.M.	Nov. 21	48 ,,	P.M.
July 8	1 ,, 25 ,,	A.M.	Nov. 24	2 ,, 9 ,,	P.M.
July 9	10 ,,	A.M.	Nov. 28	5 ,,	P.M.
July 18	1 ,, 10 ,,	P.M.	Nov. 29	35 ,,	P.M.
Aug. 11	5 ,,	A.M.	Dec. 10	20 ,,	P.M.
Aug. 12	5 ,,	P.M.	Dec. 15	35 ,,	P.M.
Aug. 15	15 ,,	P.M.	Dec. 16	1 ,, 15 ,,	P.M.
Aug. 28	50 ,,	P.M.	Dec. 17	1 ,, 30 ,,	P.M.
Aug. 29	1 ,, 3 ,,	P.M.	Jan. 8	15 ,,	P.M.

It appears, then, that two to seven paroxysms occurred in a month ; usually three or four. The intervals between them were irregular, and their duration varied from five minutes to five and one-half hours. No predisposing cause for them could be ascertained.

The patient has indefinite premonitory signs before the onset of some of the attacks. Sometimes he has abnormal sensations at the sternal notch as of contraction — not throbbing, but an occasional thump. He has felt this sensation for three days before a paroxysm, but, on the other hand, it need not be followed by one. At other times he has a sensation of soreness, not of pain, in the region of the left mamma. When a paroxysm is associated with it, this sensation is likely to persist. Although these premonitions exist, they bear no unvarying relation to the paroxysms. The onset of the paroxysms is always abrupt. The attack is characterised by a feeling of anxiety, of palpitation and slight dyspnœa. He is flatulent and expels quantities of gas. The pulse rate is 170 to 180.

After the termination of a paroxysm, which is always sudden, the patient describes a number of abnormal symptoms, such as the feeling at the sternal notch and the mammary soreness, which have been mentioned. Besides, pain just under the gladiolus of the sternum may be present when he lies on his back, but disappears when he turns to either side. Increase in urination both during and after attacks occurs.

Physical examination. He was rather obese.* The area of cardiac dulness extended 17 cm. to the left and 4 cm. to the right of the midsternum. The second aortic sound was accentuated. A soft systolic murmur was heard occasionally at the apex and also at the base of the heart. The abdomen was fat and distended. The liver was not felt. There was no œdema. The urine was normal. Systolic blood pressure was 160 mm. Hg.. The average systolic blood pressure in 1910 (fourteen estimations) was 157 mm. (on July the 27th, 1910, during an attack, the pressure was 140 mm., immediately afterward, 135 mm.), in 1911 (six estimations) 188 mm., in 1912 (six estimations) 211 mm.. On September the 4th, 1912, it was noticed that the arteries had become definitely thicker and harder since the earlier examinations. The urine contained a trace of albumin and some hyaline and granular casts. It was supposed that chronic nephritis was present. A gastric analysis was made and the stomach contents found to be normal.

On December the 17th, 1912, the patient presented himself at the hospital in a paroxysm. He described his sensation as being one of fear, and said that an abnormal feeling was present in the upper part of his chest in front. In spite of the sensation of thoracic pressure, he had no dyspnœa. He felt " uncertain," but had walked to the hospital in relative comfort. Electrocardiograms were made during the paroxysm. Then an effort was made to stop the paroxysm by pressure on the vagus nerve. Digital pressure on the left vagus nerve was made several times without effect ; pressure on the right vagus nerve succeeded in arresting the attack after two seconds. The patient was immediately aware of the change and his symptoms left him at once. He knew from the thumping sensation that terminated the paroxysm that a return of the attack was not to be expected, and, in fact, it did not recur.

An examination of the heart after the paroxysm showed the right border to be 1·5 cm. from the midsternal line and the left border 12 cm. from the median line in the fifth space. The sounds at the apex were distant. The second sound was accentuated. At the base the second sound at the aortic area was accentuated. The liver was not felt. There was no œdema. The systolic blood pressure was 182 mm. Hg., the diastolic 125 (auscultatory method). Bending at the waist several times caused an adventitious sound to appear at the apex after the first sound. There was doubt as to whether this sound was a reduplication or a systolic murmur. Three to five minutes later it was gone.

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* We are indebted to Dr. Tasker Howard for these notes.

On January the 8th, 1913, the patient reported that he had been seized with an attack the night before. He finished what he was doing and then went to lie on his bed. Then he pressed his right vagus nerve at the same spot where pressure had been exerted by us, and found that the paroxysms terminated with the same subjective symptoms as before. On January the 21st, 1913, he was examined again in a paroxysm exactly like that described; left vagus pressure failed twice, but right vagus pressure succeeded immediately in stopping the paroxysm. On January the 28th, 1913, he came again to the hospital in an attack; on this occasion, the only one in which it succeeded, pressure on the left vagus nerve terminated the attack. The mechanism attending this stopping of the paroxysm differed from that observed on the several occasions when the paroxysm was stopped by pressure on the right side. But it was not only vagus pressure that was effectual in stopping the paroxysms, for on two occasions (April the 9th and November the 15th, 1912) one or several deep respiratory movements succeeded in producing the same result. No difference between the two nerves was found to exist on pressure, when the rate and mechanism of the heart was normal. The conduction time was not lengthened by pressure on either side.

An examination of the curves made both during the tachycardial and during the normal periods on December the 17th and 26th, 1912, and on January the 21st and 28th, 1913, shows a fair degree of constancy. The nature of the paroxysms remained unaltered. Except for minor differences, to be pointed out, the outline of the complexes in each lead at the normal rate (Fig. 1) and in the paroxysms (Fig. 2) show very close similarity (Table I).

TABLE I.

Number of Curve and Leads	Slow Rate.						Paroxysm.					
	Rate.	P-R	Q	R	S	T	Rate.	P-R	Q	R	S	T
467 I	69·0	0·19	1	7	2	3	171·2		1	7	4	4
II			0	2	1	1		0·17	0	2	2	1
III		0·19	0	2	5 - 0	—1		0·15	0	1	4 - 4	—2
488 I	81·9	0·18	1	8	4	4			0	7	4	4
II	81·9	0·17	0	3	2	2	166·6	0·15	0	2	2	1
III			0	2	6+0	—1		0·15	0	1	5+4	—2
407 I			1	10	4	3						
II	63·56	0·178	0	3	2	1						
			0	2	8 - 0	—1						
493 I		0·17	1	9	4	3	174·4		1	7	5	4
II	80·0	0·17	0	2	2	2		0·17	0	2	3	2
III		0·16	0	2	7 + 1	—1		0·16	0	1	5 - 2	—2

In the first lead of the normal period, the *R* waves are tall, the *S* waves deep and wide, and the *T* waves tall and broad; in the second lead, the *R*

waves are short and the upstrokes slow, the S waves are short, but are split into deflections directed downwards, and the T waves are prominent and broad ; in the third lead, the R waves are small, the S waves deep and the returning upstrokes ascend higher than the R waves, their summits being split in two, and the T waves are broad and directed downward.

This description of the complexes in the normal period may serve as well for the paroxysmal period, with two exceptions. First, in the normal period the time from the beginning of R to the end of T is 0·37 seconds, and in the paroxysm, 0·28 seconds. The duration of the cycle is obviously contracted and the contraction takes place especially, so far as one may judge from the leads I and III, between the end of S and the beginning of T, and T itself also occupies less time. Second, an alteration is seen in the outline of the T wave in the second and third leads during the paroxysmal period. In the second lead this occurs in the upstroke of the wave, which is abrupt and steep. In the third lead, at the bottom of the T wave the round normal outline is interrupted by a small notch. The abrupt rise in the second lead of the paroxysmal curve and the notch just mentioned in the third lead, occur 0·15 seconds before the R wave in the corresponding lead. No analogue to these abnormalities is identified in the first lead. These alterations in the paroxysmal curves are interpreted to represent the incidence of the P wave. A final slight difference between the normal and paroxysmal curves is found in the first lead. Normally the bottom of the S wave is a rounded curve, but in the paroxysms, in a number of the cycles, one can detect three downwardly directed flections which deform the wave.

The appearance of the P waves at an interval of 0·15 seconds before the R waves is possible. The rhythm then is one of auriculo-ventricular sequence. This interpretation gains support from the identity between the general outline of the curves in the slow and the fast period. That the P waves represent an abnormal site in the auricular wall as the source of stimuli for the paroxysms is likely, for its shape, so far as it can be determined, bears no similarity to that of the normal P waves. The fact that the auriculo-ventricular conduction time is reduced from 0·19 to 0·15 seconds indicates, unless the property of conduction is improved during the paroxysm, that the abnormal site is at a level physiologically lower in the wall of the auricle.

Stoppage of a paroxysm by right vagus pressure was recorded (Fig. 3) on December the 17th, 1912, and on January the 21st, 1913, and by left vagus pressure (Fig. 4) on January the 28th. Left vagus pressure, as has been mentioned, failed on several (at least three) occasions when right vagus pressure succeeded ; in fact, left vagus pressure succeeded only on one occasion. The paroxysms stopped 1·6 seconds after the right vagus nerve was compressed. The post-paroxysmal pause was one second and the conduction time in the first normal cycle was 0·16. The rate gradually increased to 81·9 and the conduction time to 0·18 seconds. It will be observed that no irregularities or atypical contractions were present. Atypical beats

have, in fact, not been seen at any transition time during which this patient was observed except when a paroxysm was terminated by left vagus pressure. On this occasion, the paroxysm ceased 1·8 seconds after the left vagus nerve was compressed. In the curve a pause of 0·7 seconds follows, during which three small movements of the string are seen, and then another ventricular beat occurs, evidently of the same nature as those belonging to the paroxysm. A contraction arising in the wall of the left ventricle is seen 0·3 seconds later, and then follows, after 0·6 seconds, a wave representing an auricular beat, which is blocked, and not until 0·8 seconds later does the normal rhythm begin again. But the second beat of the normal rhythm is followed by a pause about equal to the duration of two of the first normal cycle, the pause appearing to result from sino-auricular block. The total time consumed between the beginning of vagus pressure and the beginning of orderly contractions is four seconds. In this period, then, there occurred an ectopic contraction arising in the wall of the left ventricle, a blocked auricular beat and apparently a blocked sinus impulse.

CASE 2.

History. A. J. W. is a publisher,* forty-three years of age. He is married and has had one child, who died at the age of eleven months. He had diphtheria in childhood, small-pox at the age of thirteen, malaria at fourteen, and is said to have had syphilis at nineteen. He was untreated at the time. The Wassermann reaction of the blood was made recently and was found to be negative. He has never had sore throat nor acute articular rheumatism. He had muscular rheumatism seven or eight years ago and was in bed with it for three weeks. He had pneumonia two years ago, during the course of which he had a persistent paroxysm of tachycardia. He has had palpitation on and off for twenty years. The severity and duration of these attacks vary. He has had attacks of paroxysmal tachycardia during the past five years. These attacks sometimes persist for weeks, or at least for long periods of time, but may be as short as a few seconds. When he is having short attacks, they may occur with great frequency during the day, and at night. The patient has no premonition of the onset of these attacks. He experiences palpitation, but has no pain or dyspnoea. He knows a paroxysm has ended when the palpitations cease. Sometimes at night he thinks he has averted attacks of palpitation by applying an icebag. He can usually terminate one temporarily by one or several deep breaths. However, the attack often recurs. Although conscious of the paroxysms, he is able to exert himself.

His appetite is good but capricious. There are periods when he indulges in only one variety of food. When tired of this, he changes his diet. He takes fairly large quantities of sweets. He drinks one cup of coffee a day, but no tea. He smokes about twenty cigarettes and three cigars a day, and takes an occasional drink. He is not constipated.

The patient was treated for several years for syphilis. He took mercury injections every five or six days, to relieve and reduce the number of attacks of tachycardia. The treatment succeeded for a time, but the attacks returned. Four years ago he took increasing doses of potassium iodide, three to twenty-five drops three times a day. During that time he was free from attacks of tachycardia for six months. But the paroxysms returned, and efforts to relieve them again with this drug have failed. This winter (1912-1913) he took three or four digipuratum tablets a day and thinks that they have helped him. He also took magnesium sulphate every day. He stopped smoking for three weeks, but found that he was not improving, so he resumed it. The treatment with Epsom salts continued. He has been freer from paroxysms than for some time past, but he does have a number of short attacks each day. He has been under considerable nervous strain and has led an irregular life.

Physical examination. The patient is well nourished and his colour is good. His face is pockmarked. The skin is otherwise normal. The pupils are moderately contracted, central and equal; they react fairly promptly to light. The tongue is clean. The lungs are normal. Cardiac dulness extends on the right side 3·4, 4·5 and 5·2 cm. from the median line in the second, third

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* We are indebted to Dr. Evan Evans for the opportunity of studying and reporting the findings in this patient.

and fourth spaces ; and on the left side in the same spaces 8·7, 12·0 and 13·1 cm. The heart is, therefore, somewhat enlarged. At the apex there are no murmurs, but the sounds are faint. At the base both sounds are accentuated, and there is a slight systolic murmur. Pulses are regular and the expansion is good. The liver and spleen are not felt. The abdomen is slightly adipose. Knee jerks are active.

The patient was examined twice and on both occasions electrocardiograms were taken. On the first examination, paroxysms were continuously present during a period of about two hours, but deep breaths always succeeding in stopping them temporarily. Records of the change were easily obtained. An effort to terminate paroxysms by vagus pressure was also made. It was possible to accomplish this by digital pressure of both vagus nerves, but there was a conspicuous difference in the behaviour of the two. The very lightest pressure on the left side sufficed to stop an attack, but on the right firm pressure was required. On this occasion he probably had a long paroxysm, which yielded temporarily to each of the measures we employed.

The second time he was examined (April the 24th, 1913) similar records were obtained. It was impossible to test the effect of pressure on the vagi during paroxysms then, because these ceased permanently as the result of the respiratory efforts, which were tried first. But digital pressure during the slow period showed a difference between the two nerves ; pressure on the right side was quite without effect, while on the left side stoppage of the heart for a short time and subsequent slowing were easily obtained.

A comparison of the outline of the curves made on January the 10th, 1913, with those made on April the 24th, 1913, shows them to be identical on the two dates in all three leads, for the paroxysms and also for the slow periods. The rate of the contractions in the paroxysm at the time of the first examination was 178·1, and at the second 192·7, and in the slow period 93·9 and 94·6. A comparison, lead by lead, of the curves taken during an attack (Fig. 6) with those taken when the heart was beating at a normal rate (Fig. 5), shows that the shape of the ventricular complexes has undergone a change. In the first lead in the paroxysm (Table II) the R waves are relatively tall (6 mm.) and have a notch in the upstroke, the S waves are relatively small (2 mm.) and the T waves are inverted and also small (1 mm.) In the slow period a distinct change is apparent ; the R waves are small (2 mm.) and have a notch in the downstroke, the S waves are large (4 mm.) and the T waves are upwardly directed and are well developed (2 mm.).

TABLE II.

	Lead I.			Lead II.			Lead III.		
	R	S	T	R	S	T	R	S	T
Paroxysm	6	2	-2	13		3	6	—	+2
Slow Period ..	2	4	1	9	1	+1	9	—	1·5

In the second lead in the paroxysmal period the *R* waves are tall (13 mm.) and have a sharp rise, there are no identifiable *S* waves, and there are negative *T* waves (2 mm.). In the slow period the *R* waves are smaller and the upstrokes in the first half have a very slow ascent ; there are small *S* waves (1 mm.) and positive or possibly diphasic *T* waves (2 mm.). In the third lead in the paroxysm, the *R* waves are relatively tall (6 mm.) and have a sharp upstroke and a notch in the first part of the downstroke, the *S* waves are not identified, and the *T* waves are either diphasic or directed upward (2 mm.). In the slow period the *R* waves are taller (9 mm.), have a very slow ascent in the first half of the upstroke and a sharp downstroke, no *S* waves are seen, and the *T* waves are prominent and directed downward (3 mm.). The curves obtained during a paroxysm fail to show the presence of waves which can, with any degree of certainty, be identified as *P* waves, to represent auricular contractions.

It will be seen from this comparison that the outline of the ventricular complexes during the paroxysms and during the slow periods differs. When the complexes during the slow period and during the paroxysm are identical, one does not hesitate, as in the first case, to attribute the origin of the paroxysm to a supraventricular site. When the outline of the complexes in the paroxysm differs from that in the slow periods, as in the second case, one must hesitate in assigning a cause for the change. We are still unable at the present time to decide definitely in all but a few cases on the exact site of the origin of a paroxysm. There is reason to think on the basis of the evidence suggested by Lewis[12 & 13]* that changes of some extent may be produced in the curves of a paroxysm by the rate of the stimuli. In view of these facts, even though fairly distinct differences between normal and paroxysmal curves exist, one cannot be certain whether we are dealing with a supraventricular or ventricular origin for the paroxysms. For these reasons, we hesitate to decide definitely on the site of origin of the paroxysms. Some other considerations seem, however, to indicate an infra-auricular origin for the attacks in our case, such as the occurrence of premature contractions in the ventricles, denoting an increased irritability in them.

It has already been stated that the patient could interrupt a paroxysm by a deep breath, or by several when more than one was required. These efforts sometimes succeeded, but at the end of a short period of normal beats a paroxysm recurred. Electrocardiograms of three such interruptions are reproduced (Fig. 7), one taken by the first and the other by the second lead. Apart from the stoppage and subsequent slowing of the whole heart which occurred, the curves of each lead also show the differences already described between the electrocardiograms representing the paroxysmal and the slow periods. The onset of a paroxysm is well shown in Fig. 8. A premature beat arising in the wall of the right ventricle is seen, and thereupon follow the beats of the paroxysm. The shape of the paroxysmal beats differs

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* Loc. cit., p 180

from that of the premature contraction, so that while the premature beat may have initiated the paroxysm, the paroxysmal beats are not due to impulses arising at the same point. The paroxysmal complexes are uniform and always the same, from paroxysm to paroxysm, just as in most instances of the disorder (Marris's[14] excepted). They bear no similarity to either of the premature ectopic beats (Fig. 7c and Fig. 8) observed in this patient.

Vagus pressure was successful in stopping paroxysms in this case, as has been stated. It was difficult to do so by pressing on the right side, but it was very easily accomplished by pressing on the left. Unfortunately, no records were obtained when the right vagus nerve was compressed. When the left vagus was tried, the paroxysms came to an end in the same way as they did when the patient breathed deeply. No abnormal beats were seen.

Remarks.

In the first case, the paroxysm was of supraventricular or auricular origin and yielded easily with no derangement in mechanism to right vagus compression, but usually did not yield when the left vagus was employed. And on the one occasion when left vagus pressure succeeded, the way in which the paroxysm came to an end was distinctly unusual. The second case was of doubtful, possibly of ventricular origin. The facility with which the paroxysms were stopped by left vagus pressure was in striking contrast with the difficulty experienced by pressing on the right side. It must, however, be stated that pressure on the right side accomplished its work much more easily in this patient than pressure on the left side accomplished it in the auricular case.

A number of subjects are suggested for further study by these observations. Vagus pressures should be tried in all the cases of paroxysmal tachycardia, and the attempt should not be confined to one side only ; success might follow compression of the opposite nerve. Observations of a number of cases embracing electrocardiographic study of the mechanism of the paroxysm, correlated with the study of its nerve control, are required before one can assign a successful stoppage as due to the specific effect of pressing one or the other vagus nerve.

SUMMARY.

Two cases of paroxysmal tachycardia are reported. One case is of auricular origin, and the results of pressure over the vagi indicate that the paroxysms are controlled by pressure especially over the right vagus. The other case is of doubtful, possibly ventricular, origin and the paroxysms are controlled by pressure especially over the left vagus.

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Fig. 1-4. Four electrocardiographic curves from a case of paroxysmal tachycardia, of auricular origin. In each series of three curves, the upper one is taken from Lead *I*, the second from Lead *II*, the lower one from Lead *III*. The time is marked in 0.2 seconds. The tension of the string was so arranged that 1 cm. equalled 1-1,000 volts. Fig. 1 shows the normal mechanism. Fig. 2 shows a portion of a paroxysm of tachycardia. Fig. 3. Lead is taken during right vagus pressure. Fig. 4. Lead is taken during left vagus pressure.
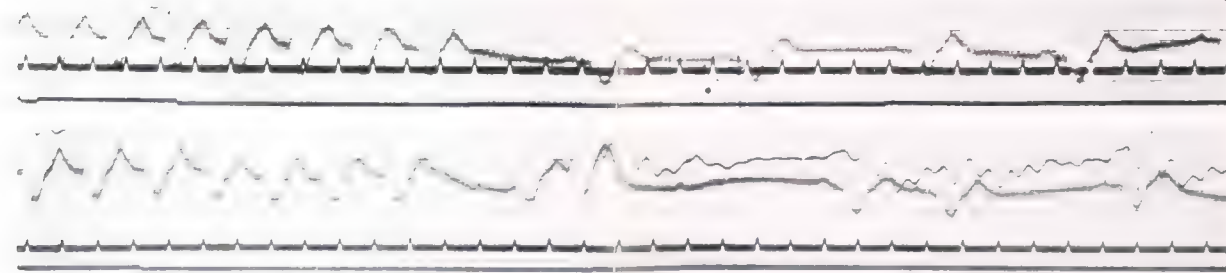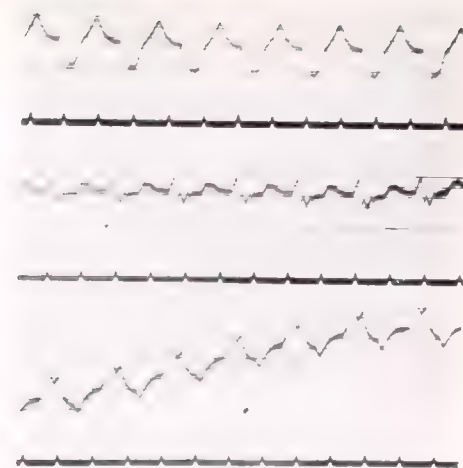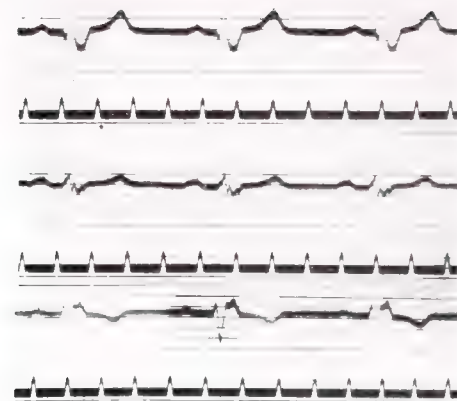
Fig. 5-6.   Four electrocardiographic curves from a case of paroxysmal tachycardia of doubtful, possibly ventricular, origin.   Leads, time marker and standardisation of the string as Fig. 1-4. Fig. 5 shows the normal mechanism.   Fig. 6 shows a portion of a paroxysm.

Fig. 7.   Fig. 7 shows three examples of the cessation of paroxysms during deep breathing :—

(a) Lead I.

(b) Lead II.

(c) Lead III.   The first beat of the normal rhythm is followed by a premature contraction.

Fig. 8.   Fig. 8 shows the beginning of a paroxysm after a premature beat.   It is continuous with Fig. 7 (c).

REVERSAL OF THE CARDIAC MECHANISM.[6]

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For a little more than a year we have had under observation a patient whose cardiac mechanism is most unusual: in fact, so far as we have been able to learn, it seems to be unique. We propose to give a brief account of our clinical observations together with some experimental data which bear on the interpretation of the clinical findings.

Clinical history.

H. M., 51 years of age, dock labourer, came under observation at the Vanderbilt Clinic on July the 15th, 1912. He stated that he had been well until three months before admission to the clinic, but subsequently it was learned that he had had a persistent diarrhœa for a year with three or four watery stools a day. Until the onset of symptoms he had been a heavy drinker. He denies lues and gonorrhœa. During the three months before admission and subsequently, he has suffered from attacks of dizziness of increasing severity. In one of these attacks he fainted and fell in the street. Muscular effort increases his giddiness, he has a good deal of headache, is very drowsy and is annoyed by tingling of the hands and feet.

Clinical observations.

The patient is a well developed, fairly well nourished man. The skin and mucous membranes have a peculiar pallor. Lungs, abdomen and extremities present no abnormality. The heart is not enlarged. The sounds are faint, but clear. No murmurs are heard. A third sound has been distinctly audible at times and has been graphically recorded. A faint low-pitched systolic murmur is evident in the sound record, but the diastolic interval is clear. The pulse is regular, forty beats per minute. The peripheral arteries are not perceptibly thickened. Systolic blood pressure varies between 95 and 110 mm. Hg. The diastolic pressure is usually about 65 mm. Blood and urine are normal. Stools contain no ova or parasites, but the amount of mucus is moderately increased. The Wassermann reaction is negative.

The symptom complex and slow pulse are suggestive of heart block. Figs. 2, 3 and 4 are the electrocardiograms of this patient. It is evident at a glance that they bear no resemblance whatever to the familiar

galvanometric picture of heart block.   On cursory examination, lead *I* gives
the impression of being a series of typical ventricular complexes without
evidence of any auricular action current.   If we take this view, leads *II*
and *III* would be regarded as successions of somewhat anomalous ventricular
complexes.   If this view is correct, two interpretations are possible as
regards the condition of the auricles : either they have altogether ceased
to beat, or they are beating at such a time that their action current is
completely submerged in that of the ventricles.   Certain peculiarities of the
curves in leads *II* and *III*, however, seem to speak against the view that
they consist entirely of anomalous ventricular complexes.   The trend of the
deflection of the shadow following the peak *R* is precisely that of the usual
wave *T* up to the time that a small sharp downward deflection occurs.   It
is this small downward deflection that gives the curve its peculiar character.
Following the completion of the anomalous part of the curve, its trend
again follows the usual course of a *T* wave so that one can scarcely escape
the conclusion that the activity of the ventricles has been in no way unusual,
but that the anomaly has been produced by the simultaneous impression
upon the string of an electrical force originating elsewhere than in the
ventricles.   The absence of the *P* wave from its usual situation suggests the
possibility that this anomalous deflection which interrupts the otherwise
smooth course of the ventricular action current may be the auricular
electrogram.   The time of its occurrence, about ·18 second after the beginning
of the ventricular electrogram* is further suggestive, since this is practically
identical with the normal conduction time between auricles and ventricles.
If, however, the auricles begin their activity ·18 second after the beginning
of ventricular contraction, some evidence of their action current should be
discernible in lead *I*.   In leads *II* and *III* the small inverted waves have
nearly the same amplitude, and according to Einthoven's subtraction rule
we should not expect the corresponding wave in lead *I* to be large.   On
examining closely the curves of lead *I*, small but definite oscillations can be
distinguished, beginning about ·18 second after the beginning of the ventricular
curve.   These oscillations are fairly constant from cycle to cycle and can
be seen especially well with the help of a lens.

   The above interpretation of the anomalous part of the curve would
receive material support from any evidence which might be adduced to prove
that the auricles actually contract.   Such evidence we have been able to
secure by direct examination with X-rays and the fluoroscope.   If one uses
a powerful tube and places the patient at a distance of about two meters
in front of the tube in close contact with the fluoroscope, the lack of sharpness
at the edges of the shadows is largely avoided.   The procedure is similar
to that commonly employed in orthodiagraphy.   It is desirable that the
observer remain in the completely darkened room for a sufficient length of

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* This time varies somewhat and is shorter in lead *III*.   Comparison of the heights of *R*
in the three leads suggests considerable phase difference.

time to permit the retinæ to become adapted to darkness. The outline of the contracting auricle can be sharply distinguished in nearly every case. In the case under discussion the contractions of the auricle could be distinctly seen. It is not possible to determine the relative time of contraction of auricles and ventricles with any considerable degree of accuracy by this method. The observations can best be made on the right margin of the right auricle and the left margin of the left ventricle, and these edges are too far apart to be observed by one person without changing the point of fixation.

The view that the ventricular complexes in this case are typical curves, distorted by the occurrence of an unusual *P*, receives further support from the record shown in the accompanying figure (Fig. 1). Here in the third and
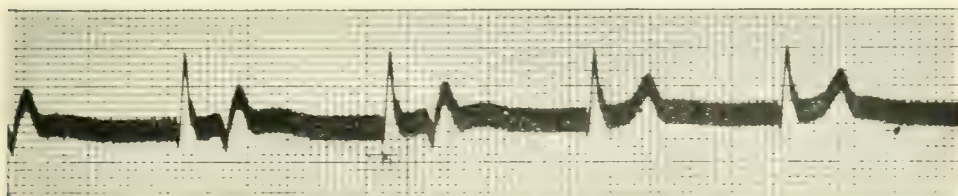
Abscissa, 1 division = ·04 second.
Ordinate, 1 division = 10⁻⁴ volt.
Fig. 1.—The conduction time is unusually long, compare Fig. 3.

fourth complexes, conduction seems to have failed. Except for the absence of the small downward deflection, the last two complexes differ but slightly from the first two. We have other records which show occasional isolated complexes in which the small downward deflection is absent.

In discussing this case at the laboratory we have found it convenient to define a property of heart muscle which appears to be generally recognized, though it seems thus far to have escaped a specific nomenclature. It is a familiar fact that when the physiological connection between auricles and ventricles is interrupted the chambers beat at different rates. The rate of the auricles remains about the same as before, that of the ventricles becomes much slower. We believe the facts justify the assumption that the tendency to beat at the slower rate is always present in the ventricles. We wish to distinguish clearly between the tendency to beat at some particular rate and the actual rate of beat. The latter may be the result of control exercised by another chamber whose inherent tendency is different. This property of heart muscle bears considerable analogy to the familiar natural vibration period of physical bodies. Suppose a short pendulum with a heavy bob connected by a horizontal link bar to a long pendulum which has a light bob. When the system is set in motion the short pendulum oscillates at its natural period since its bob is supposed to be so heavy in comparison with the other that its momentum shall control the system. The long pendulum executes

forced oscillations at the same rate as the short one ; that is the long pendulum swings at a rate faster than its natural period. If the connecting bar is removed, both swing at their natural periods, the long one slower than the short one. The particular rate at which a pendulum tends to oscillate is what is called its natural period. To denote the *tendency* of a chamber of the heart to contract at a particular rate, possibly at a rate quite different from the actual rate of beat, we have no single term. We suggest that the word " period " used in a sense analogous to the physical expression " natural period " may be found convenient to designate this tendency.

When complete heart block occurs in man the ventricular rate is usually in the neighbourhood of thirty per minute, sometimes a little faster and sometimes slower. Presumably the ventricles always have the tendency to beat at approximately this rate ; this is their period. The customary heart rate of something like seventy beats per minute is, so far as the ventricles are concerned, a forced rate and depends on the period of the auricles. The period of the auricles may be affected in various ways, notably by influences emanating from the vagus. Changes in the auricular period generally affect the rate of the entire heart. The period of the ventricles may fluctuate over a considerable range without affecting the heart rate. When the ventricular period is higher than that of the auricles the ventricles may be expected to control the rate of the heart provided that the ventricular impulses can pass backward to the auricles.

During the last few months, accompanying an improvement in the patient's general condition, an increasing tendency toward return to a normal cardiac mechanism has been observed. This is in striking contrast to the constancy of the reversed mechanism shown during the early months. The records shown in Fig. 5 and 6 were taken in succession within a few minutes of each other. Some of the peculiarities of these two successive records of the same lead would be difficult to understand without keeping in mind the notion of an independent period in auricles and ventricles. In Fig. 6 the mechanism is reversed, the ventricles are in control. The rate of the heart so determined is constant within ·03 or ·04 second. In Fig. 5 the auricles are in control and conduction takes place in the usual direction. It is of interest to note that the *P-R* interval is almost precisely the same as the *R-P* interval of the reversed mechanism. Reversed conduction is usually held to be more difficult and to require more time than direct. Here it seems to occur at the same rate in either direction. The heart rate when the auricles are in control is seen from Fig. 5 to be much less constant than in the reversed condition. A maximum variation of ·12 second occurs in this record. As might have been expected the average rate is more rapid than when reversed, though not much more rapid. The practical constancy of the ventricular period and the variability of that of the auricles suggests that a lowering of the auricular period may be responsible for the reversal of the mechanism. As possible causes for such a lowering of period one might think of a lesion of the auricle or of interference with its blood supply,

or of nervous or toxic disturbances. The etiological relationship of an anatomical lesion to reversal of the mechanism of the heart can be only a matter of pure surmise until such a case shall have been studied not alone in the clinic but in the deadhouse. If the condition were of nervous origin it would seem probable that it would be found to depend on abnormally powerful vagus control. It is well known that vagus control can be diminished or abolished by administration of atropin. During the second week that the patient was under observation, atropin was administered in full physiological doses. It was given by mouth for three days and on the third day additional atropin was given subcutaneously at the laboratory. Despite the fact that the usual effects of atropin were well marked, there was no change at all in the rate or mechanism of the heart and electrocardiograms taken at this time were identical with those taken before atropin was given. We have no evidence which points toward a toxic origin of the disturbance, but pending the determination of the presence or absence of lesions in the case it may be well to bear in mind the chemical possibilities.

So far as we are aware no case of bradycardia exactly comparable with the one above described has been reported. It seems altogether probable, however, that the condition has occurred before, as it might easily have escaped differentiation from other bradycardias unless investigated by some of the more recent graphic methods. We find in the clinical literature two references to reversal of conduction in the heart. Both are of recent date. Norrie and Bastedo[5] have reported a case of heart block in which, following digitalis medication, the pulse during short intervals doubled in frequency. From a polygraphic tracing secured during one of these intervals they concluded that a reversal of the mechanism occurred. The condition was transient. Hart[4] has reported a case of paroxysmal tachycardia in which the tachycardia seems to have been determined by a rise in ventricular period. The electrocardiograms indicate that a reversal of the mechanism has taken place.

Experimental observations.

In planning the experiments we have not attempted to investigate all of the conditions under which reversal of conduction may take place, nor have we attempted to settle experimentally the question of clinical etiology. The latter, it seems to us, can be accomplished only by complete investigation of clinical material. However, as a check upon conclusions drawn from clinical study, it seemed worth while to determine the form of the electrocardiogram in experimental retrograde conduction. The experimental procedure consisted in destruction of the part of the right auricle corresponding to the region of the sino-auricular node. The destruction was usually accomplished by crushing, sometimes by excision. This procedure has been extensively used with various modifications in studying the function of the

sino-auricular node region [2,3,4,5,7]*   Dogs were used as the subjects of experiment.   Ether anæsthesia was maintained throughout the experiments and at the end the animals were killed with chloroform.   During the period of experimentation the animals were kept warm by the application of external heat, and the mixture of air and ether vapour used in artificial respiration was moistened and warmed to the temperature of the body.   Conservation of the animal's heat is of importance in studying the electrocardiogram. Without it movements of the leg muscles are apt to occur, even under profound anæsthesia.   Such movements introduce complicating action currents which may confuse the records.   All the experiments were carried out with the heart *in situ* and the circulation intact.

In every experiment the production of the lesion was followed by a slowing of the heart rate.   In all cases the auricles continued to beat, sometimes after momentary stoppage.   The most usual result of the operation was the simultaneous action of auricles and ventricles.   This frequently gave place to the auricle-ventricle sequence.   During the time that the auricles and ventricles beat simultaneously no trace of a *P* wave can be seen in the electrocardiograms.   As the auricles gain precedence the *P* wave seems to " emerge " from the *R* wave and gradually comes to lie further and further in front of *R* until a normal *P-R* interval becomes established.   After this occurs, despite destruction of the region of the sino-auricular node, the electrocardiogram looks very much like that of a normal dog, except that the rate remains rather slow.   On several occasions instead of simultaneous contraction of all chambers, the ventricles preceded the auricles.   Typical electrocardiograms from two such experiments are shown in Fig. 7, 8, 9 and 10.   On each of these occasions and on none of the others the highly characteristic curves obtained from the patient were reproduced in all their essential features by the dogs.[1]

Summary.

A patient with slow pulse and symptoms of Stokes-Adams disease has been studied.

The condition is not heart block.

The form of the electrocardiograms is unique.   The diastolic interval is a smooth unbroken line, while the ventricular electrocardiogram is distorted by the occurrence of *P* about ·18 second after the beginning of *R*.

Investigation with X-rays has shown the auricles to be active.

The condition has persisted over many months, latterly there have been periods of variable duration during which the heart rate has increased.   At such times the electrocardiogram has reverted to the ordinary typical form.

Atropin is without effect on heart rate and mechanism.

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* Further references to the literature of this subject can be found in the articles cited.   We refrain from discussion of the literature as it would necessarily involve consideration of much unrelated matter.

When reversal of the cardiac mechanism is produced in dogs the form of the electrocardiograms resembles in all essential particulars the highly characteristic curves of the patient.

Conclusion.

Reversal of the cardiac mechanism is a clinical entity, it may persist for a long time and yields an electrocardiogram whose form is characteristic.

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DESCRIPTION OF FIGURES.

In Fig. 2 to 8 inclusive, the abscissa divisions correspond to a duration of ·04 second   In Fig. 9 and 10 the abscissa divisions have a value of ·02 second.   The ordinate divisions have the value 10^{-4} volt in all the records.

Fig. 2, 3 and 4 are leads *I, II* and *III* of H. M.   In addition to features noticed in the text, the prominence of the wave *u* is remarkable

Fig. 5 and 6 are both lead *II* of the patient, H. M , taken within a few minutes of each other.   Notice that peak *R* is higher with the reversed mechanism.

Fig. 7 to 10 are experimental records, all are leads from the right fore leg and left hind leg. Fig. 7 and Fig. 8 are from the same dog. Fig. 7 a record taken before crushing the sino auricular node and Fig. 8 one obtained immediately after crushing   In Fig. 8 an artefact caused by the apparatus for artificial respiration occurs at points marked X.   Fig. 9 and 10 are records similarly obtained from another dog before and after crushing the region of the sino-auricular node   To facilitate time measurements the plates were run at double the rate of those used in the preceding records.

In both sets of experimental records the marked slowing of the heart rate after crushing the sino-auricular node is well shown   The height of *R* in the reversed condition is greater than in the normal records, as was also the case in the clinical records.

Experimental work now in progress has thrown some light on this phenomenon but the results are not yet ready for discussion.   In Fig. 10 a well-marked wave *u* can be distinguished.
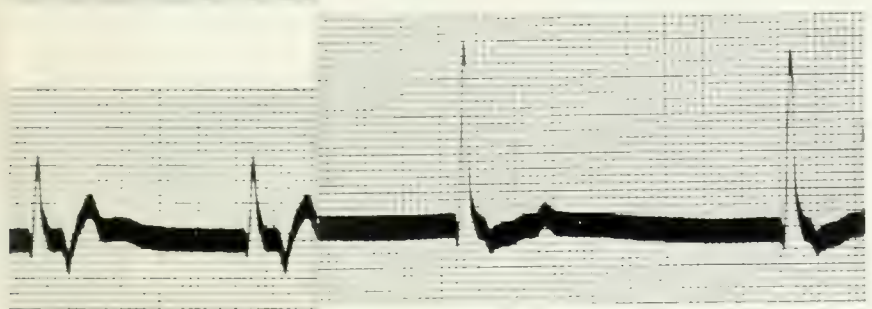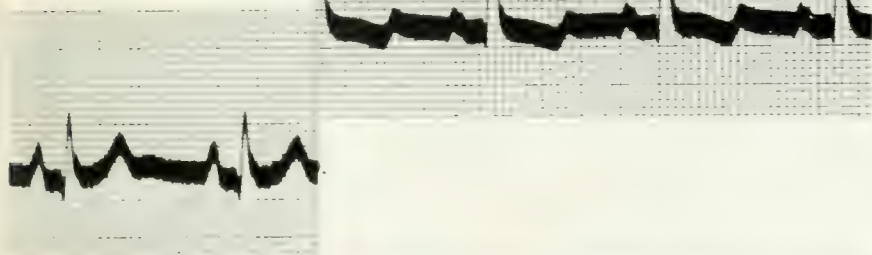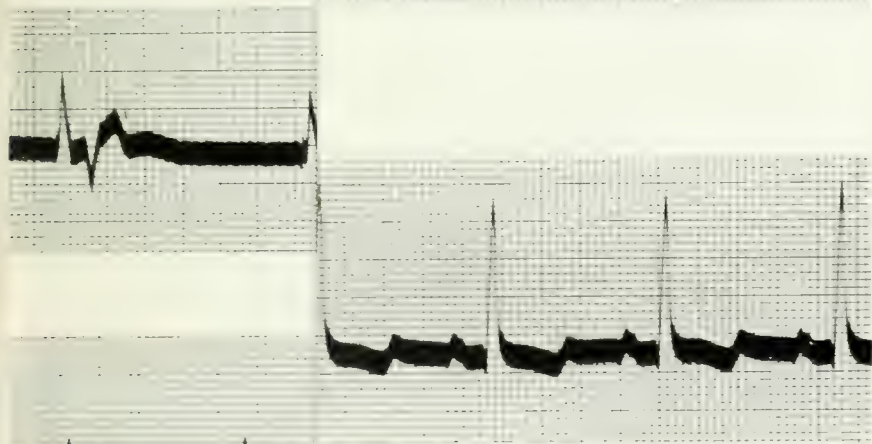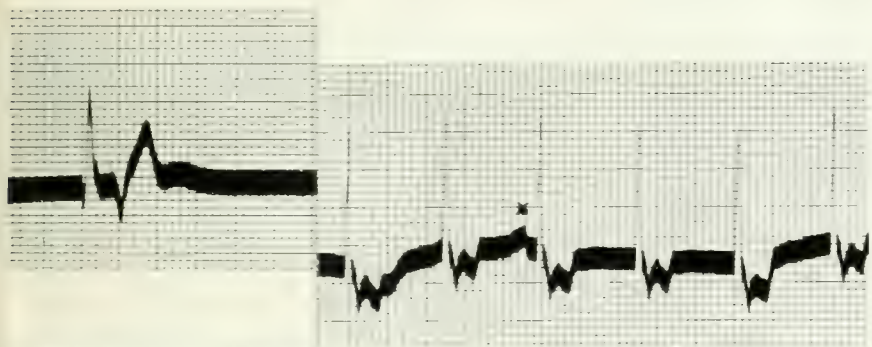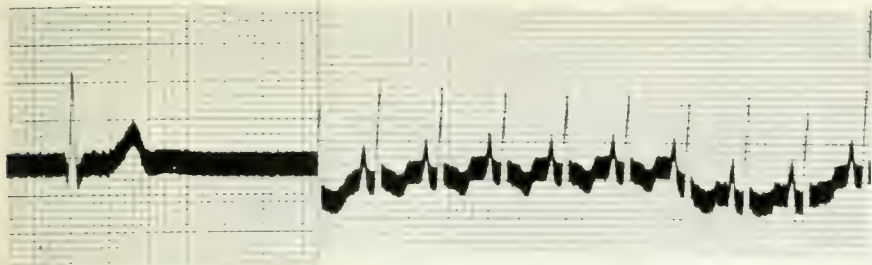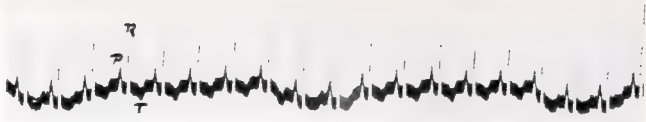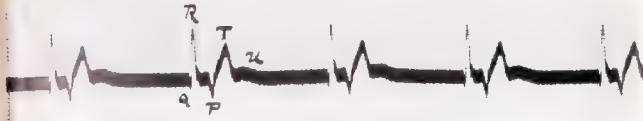
EXPERIMENTS ON THE ORIGIN AND PROPAGATION OF THE IMPULSE IN THE HEART.

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THE POINT OF PRIMARY NEGATIVITY IN THE MAMMALIAN HEART AND THE SPREAD OF NEGATIVITY TO OTHER REGIONS.

Introduction.

THE experimental work which we have carried out in this field was undertaken in an attempt to obtain additional evidence regarding the place of origin of the cardiac impulse in the normal heart, to find the physiological connections of this region with other parts of the heart, to determine those regions which assume the function of automaticity when the normal pacemaker is removed and to study the influence of the extrinsic cardiac nerves on the automaticity of different regions. The results from this work we hope to report in a series of papers. In most of this work up to the present time, we have used the galvanometric method of attacking the problem, a method previously employed by Wybauw, by Lewis, Oppenheimer and Oppenheimer, and by ourselves in work on the heart. The fact that a wave of relative electric negativity accompanies activity in nerve and muscle has been known for many years, and the view that initial negativity is coincident in time and place with initial activity of the living substance has received abundant support, and, so far as we know, has never been denied.

Historical.

The discovery of the auriculo-ventricular node by Tawara[25] in 1905, and the description by Keith and Flack[12] a year later of similar tissue lying in the sulcus terminalis of the right auricle and forming the sinus node, stimulated a number of experimental contributions in an attempt to determine the physiological importance of the tissue forming these nodes, which differs histologically from ordinary cardiac muscle. The methods which have been employed in these studies include (1) injury to, destruction or excision of the sinus node (Jaeger,[11] Magnus Alsleben,[19] Hering,[10] Cohn, Kessel and Mason,[3] Moorehouse,[23]) or the action of various influences upon it (Flack,[8] Brandenberg and Hoffmann,[2] Ganter and Zahn,[9] and Zahn[28]); (2) the determination of comparative rhythmicity in cardiac strips containing, and those not containing, nodal tissue (Erlanger,[5] Moorehouse[23] and [24]); and (3) the relation of the sinus node to the normal seat of the origin of the cardiac impulse as

determined by galvanometric curves or by electrocardiograms (Wybauw,[27] Lewis,[16] Lewis, Oppenheimer and Oppenheimer[17]). The experimental results, as interpreted by different workers, have led to a number of different views in reference to the importance of the sinus node ; (1) that it represents the region in which the cardiac impulse normally arises (Wybauw, Lewis, Lewis, Oppenheimer and Oppenheimer, Brandenberg and Hoffmann, Ganter and Zahn) ; (2) that it represents a region mainly concerned with the control of the extrinsic cardiac nerves (Flack) ; (3) that the sinus node has no essential importance not shared by other tissue in the regions surrounding the node (Jaeger, Magnus Alsleben, Erlanger, Moorehouse) ; (4) that the node and connections represent a sensory mechanism, essentially similar to the muscle spindles of Kühne and Sherrington and serving the function of the reception of sensory stimuli necessary for co-ordinated heart activity (Mackenzie[18]). The anatomical researches of Koch,[15] Keith and Mackenzie,[13] Mall,[20] and others, have shown that the sinus node, auriculo-ventricular node and associated structures, occur in the hearts of all mammalia, and to a less developed degree in amphibia and reptiles, and are to be regarded as remnants of primitive structures which no longer exist as such in the adult mammalian heart (sinus venosus and auricular canal).

The experimental work that will be described in this paper was carried out with the aid of the galvanometric method. Detailed reference will be confined to preceding work on the mammalian heart in which this method was employed. The large literature concerning the origin of the cardiac impulse and its propagation over the heart as studied by various methods will not be reviewed in detail at the present time. References to this literature may be found in the papers referred to above or in the recent review of this subject by Erlanger.[6]

An attempt to localise the point of origin of the heart beat in supra-ventricular regions of the heart by determination of the region which first manifests electrical negativity in the normal beating heart, was first made by Wybauw.[27] Using the Einthoven thread galvanometer, he found that an area along the veno-auricular sulcus (sulcus terminalis), corresponding to the position of the sinus node as described by Keith and Flack, manifests electric negativity in the dog's heart *in situ* before the mouth of the superior vena cava or the right auricle. He found that the negativity spread rapidly to the right auricle and that no sino-auricular interval, comparable to the auriculo-ventricular interval, was present. Strong stimulation of the vagus abolished temporarily the power of the sinus node to initiate impulses, and under these conditions the impulse arose in some other region, but always in the immediate neighbourhood of the node. A repetition and extension of this work with careful histological control was made by Lewis, Oppenheimer and Oppenheimer,[17] who also worked on the dog's heart *in situ*. Non-polarisable electrodes were applied to the surface of the exposed heart, and in the different experiments nineteen different points were compared as to initial negativity. These places were marked and afterwards examined

histologically for the presence or absence of nodal tissue. Seven points along the sulcus terminalis, six points on the superior vena cava, four points on the body and appendages of the right auricle, and two points on the pulmonary veins were investigated. The upper end of the sinus node near its widest part was found negative to all other points on the node and elsewhere in six of seven experiments. In one experiment a point at the mouth of one of the pulmonary veins was negative before the sinus node, while the node was negative before all remaining regions.

Methods.

The experiments which will be reported in this paper were all done on hearts *in situ*. Nearly all the experiments were performed on dogs, the few experiments on rabbits and cats are noted in the descriptions. The thorax was opened under artificial respiration with ether anæsthesia, in such a way as to obtain as good an exposure as possible of the regions of the heart comprising the right auricle and entering veins. The air used in artificial respiration was warmed by passing through a heating coil and the normal temperature of the animal was maintained as far as possible by this and by the use of hot water bags applied to the animal. The positions on the surface of the heart to which it was desired to apply electrodes were marked by laying fine silk ligatures. The electrodes employed were of the zinc-zinc sulphate type and were supported by adjustable holders. From the end of each electrode a thread of woollen yarn about one millimeter in diameter projected, and the ends of these were held by means of the ligatures to the surface of the heart. The threads were sufficiently long to permit free movement with the heart, and care was taken that the contact with the heart should comprise only an area of about the diameter of the thread. The electrodes were connected through suitable apparatus with a string galvano-meter of the large electromagnetic type (Edelmann model), in which a quartz fibre was used in all experiments. In most cases the sensitiveness of the galvanometer was not determined, but this was adjusted until satisfactory records were obtained. In those cases where it would seem to be of importance the sensitiveness was determined by the usual procedure. Photographic records were made on bromide paper. In all cases suspension curves of the right auricle alone or of the right auricle and right ventricle were simultaneously recorded. In some experiments these were recorded on the photographic paper with the galvanometer curves, in others separate records were made on a Hürthle kymographion. In the latter an electro-magnetic signal recorded on this and on the simultaneous photographic record, so that corresponding points on the two curves could be identified. In this way identical cycles were readily determined. At the end of the experiments the electrodes were removed, leaving the ligatures in place, the hearts removed *in toto*, fixed in formalin and later transferred to alcohol for the purpose of either macroscopic or microscopic examination as to the position of the electrodes as marked by the ligatures.

In most experiments an electrode was applied to the lower portion of the inter-auricular septum in the region of the auriculo-ventricular node. This was done by passing a long curved electrode down through the external jugular vein, superior vena cava and right auricle and adjusting its position until its point was in contact with the desired region. It was then secured in place by a holder. In a few experiments electrodes were placed, by a similar procedure, in contact with the inner or endocardial surface of the sulcus terminalis (tænia terminalis) or of the right atrium. The point of contact of the electrode was determined at the end of the experiment and marked by a ligature.

The galvanometric curves were for the purpose of determining the region which manifested initial negativity and the sequence of propagation of negativity to other regions. The suspension curves served for accurate interpretation of the galvanometer curves and for the determination of the period and sequence of auriculo-ventricular conduction and its modification under experimental procedures. In all experiments electrocardiograms[*] were also made by connecting the galvanometer through suitable electrodes with the right anterior and left posterior limbs (lead II of Einthoven). These were of importance in determining changes in the P-R interval and in indicating by their similarity to or divergence from the normal type of electrocardiogram whether the heart was contracting normally or otherwise.

Determination of which one of any two points showed initial negativity was made by two methods. In some experiments only one of these methods was used, in others both were used. The first of these two methods is one previously employed by Wybauw and by Lewis, Oppenheimer and Oppenheimer in mammalian heart work, and by ourselves in a study as to the origin and propagation of the wave of negativity in the tortoise heart. It has been extensively used in work on skeletal muscle and on nerve. It consists in connecting the two regions which are to be compared through the galvanometer and determining which first manifests negativity by the direction of initial movement of the galvanometric curve. The direction of movement where one electrode is made negative to the other is previously determined. The second method consists in the determination of the relation of onset of negativity in two or more regions to the onset of mechanical systole of the auricle. Electrodes of the usual type are placed on the regions to be compared and connected through a multi-point contact switch with one pole of the galvanometer. A large indifferent electrode is placed on some part of the body, usually on the left posterior limb and connected directly with the other pole of the galvanometer. A record is then made in which each electrode on the heart is connected in turn through the switch and galvanometer with the indifferent electrode and the instant of movement

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* It seems advisable to confine the term electrocardiogram to include curves arising from the sum of all the action currents developed by the heart, as obtained by leading off to the galvanometer from body tissues outside the heart or from two points widely separated on the heart. The curves obtained from two leads on a single chamber show varying degrees of resemblance to the electrocardiogram as above defined.

of the curve indicating negativity of the former compared with the onset of mechanical systole of the auricle, as recorded on the same record by suspension or by an electric signal actuated by the contracting auricle. This method has the advantage over the first method described in that the time interval from the appearance of negativity in one region to its passage to another may be estimated. The method of initial negativity between two electrodes on the heart has also been used to estimate conduction, but is subject to errors which we believe render it valueless for this purpose, as will be discussed later. The main source of error in the method of comparison with auricular systole consists in determining with exactness the onset of mechanical systole, common to all graphic curves taken on a rapidly moving surface and also to possible variation in tonus of the auricle, especially in experimental procedure.* Care was taken to obtain as good suspension records as possible and to consider only those in which the onset of auricular contraction was sharply marked on the record. In all cases in which this method was employed the speed of the record was such that 1 mm. corresponded to ·005 sec.; sufficiently fast to allow accurate measurements to ·0025 sec. or less. In the use of the first method records were made at a slower speed, sufficient to give curves in which the initial movement was clear, usually such that 1 millimeter corresponded to about ·02 sec.. In most of the experiments in which this method was used, a specially devised switch was included in the circuit, by means of which any two electrodes desired could be connected through the galvanometer by a single movement.

The region of primary negativity in the mammalian heart, and the conduction from this region to surrounding parts.

We have employed both of the methods described above in an attempt to determine the region of primary negativity. Our results confirm the previous findings of Wybauw,[27] and of Lewis, Oppenheimer and Oppenheimer,[17] that initial negativity in the dog's heart is manifested on the surface of the heart over a region corresponding anatomically to the position of the sinus or Keith-Flack node. In 38 experiments on dog's hearts *in situ*, some part of the sinus node was found to precede in negativity one or more regions lying outside in all cases. In eight experiments we compared regions at different levels of the node and of the venous and auricular tissues lying immediately contiguous to the node. The position and extent of the node and its relation to the points compared was carefully controlled in all these by histological examination. In four of these experiments the onset and propagation of negativity was determined by the first method described above, in the remaining four the time intervals of the spread of negativity was estimated by the second method. The results from these experiments are described below. Description of the four experiments by the first method will be given first.

* A better method would be a comparison of two galvanometric curves simultaneously recorded by two galvanometers connecting different electrodes. We hope to apply this method in the near future to a more accurate determination of time intervals of conduction.

The position of the electrodes and the position and extent of the node are shown in the diagram (Fig. 1), which was drawn to scale from serial sections.

Fig. 1.

Histological examination showed the position of the electrodes to be as follows :—

Electrode 1.   On auricular edge of node near upper end.

Electrode 2.   On the auricle, 3 mm. from the edge of the widest part of node.

Electrode 3.   On the node, slightly below widest part.

Electrode 4.   On the venous edge of node, at widest portion.

Electrode 5.   On the mouth of the superior vena cava, 3 mm. from edge of node.

Electrode 6.   On sulcus terminalis, 3 mm. below lower end of node.

The curves show that electrode 3 was negative before all other regions. The relations are expressed diagrammatically in the accompanying figure (Fig. 2). The points of contact of the electrodes are represented by small circles and numbered as in the previous diagram. The lines connecting the different circles indicate that a comparison was made between the two regions, and the crosses on the lines indicate which showed initial negativity.

The electrode on the node, somewhat below its widest part (3), showed negativity before the others. It is to be noted, however, that the negativity spread to the venous edge of the node above (4) and out on to the superior vena cava above the node (5) before it reached the auricular border of the upper end of the node (1). Thus, while there was one point on the node (3) which was negative before all other regions, the negativity spread out from the node to involve certain regions outside the node (5) before it involved all parts of the node itself (1). It should be noted that electrode 1 just touched the edge of the node on its auricular border and all our evidence as will be seen later, indicates that spread of negativity from the node to the auricle is relatively difficult as compared with its spread to other parts.
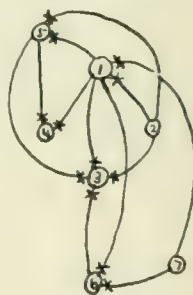
Fig. 2.

Similar in every way to the above. The extent of node and position of electrode is shown in Fig. 3. The electrodes were placed as follows :—

Fig. 3.

Electrode 1.   At middle of node at widest portion.

Electrode 2.   On middle of lower third of node.

Electrode 3.   On sulcus terminalis, below node.

Electrode 4.   On auricle, 3 mm. from node.

Electrode 5.   On venosus side of node, about 4 mm. from border of node.

Electrode 6.   On mouth of superior vena cava, about 5 mm. from border of node.

The relative negativity of these different regions is shown in Fig. 4. The order is as follows :

Initial negativity near mid-region of node at widest point (electrode 1).

Venous side of sinus node (electrode 5).

Mouth of superior vena cava (electrode 6).

Lower third of node (electrode 2).

Sulcus terminalis below node (electrode 3).

Right atrium near node (electrode 4).
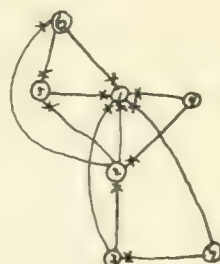
Fig. 4.

Experiment of April the 7th, 1913.

Fig. 5 shows extent of node and position of electrodes. Fig. 6 shows the order of negativity as follows :—

Initial negativity in mid - region of main part of node (electrode 1).

Venous side of node, 3 mm. from border (electrode 5).

Mouth of superior vena cava, 2 mm. above node (electrode 6).

Right auricle, 3 mm. from border of node (electrode 4).

Sulcus terminalis below node (electrodes 2 and 3).

Fig. 5.
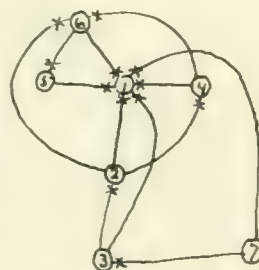
Fig. 6.

Experiment of April the 10th, 1913.

Fig. 7 and 8 show the position of the electrodes and the spread of negativity. This is as follows :—

Initial negativity on main part of node (electrode 1).

Lower one-third of node (electrode 2).

Venous tissue bordering on mid-region of node (electrode 4).

Sulcus terminalis below node (electrode 3).

Mouth of superior vena cava, 4 mm. above upper border of node.

Right auricle, 5 mm. from edge of node near mid-region.

Fig. 7.
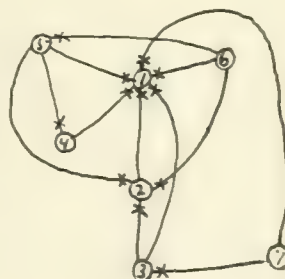
Fig. 8.

The following are four experiments by the second method described above and comprise measurements of intervals by conduction in these regions.

Experiment of February the 15th, 1912.

Seven electrodes were placed on the heart. The position of these as determined by serial sections was as follows :—

Electrode 1. Mouth of superior vena cava, 8 mm. from border of node.

Electrode 2. Vena caval border of upper end of node. Does not touch nodal tissue.

Electrode 3. Auricular border of upper end of node. Does not touch nodal tissue.

Electrode 4. Auricular border of lower end of node. Does not touch nodal tissue.

Electrode 5. Auricular appendage, about 6 mm. from upper end of node.

Electrode 6. Vena caval border of mid region of node.

Electrode 7. Auricular appendage at border of node.

None of these electrodes was in contact with nodal tissue. Electrode 2, on the vena caval border of the upper end of the node showed first negativity, preceding the auricular side of the node (3 and 7) by ·005 to ·01 sec. and the venous side of the node lower down by about the same interval. The auricular border of the lower end of the node (4) followed the venous border of the upper end by ·015 sec.

Experiment of February the 22nd (A.M.) 1913.

The electrodes and spread of negativity was as follows :—

Electrode 1. On upper portion of sinus node. This electrode showed first negativity.

Electrode 2. On mid-region of sinus node. Negativity occurred here ·005 sec. after its appearance in electrode 1.

Electrode 3. On venous side of node, about 2 mm. from its edge. This followed the upper end of node by about ·01 sec..

Electrode 4. On auricle, about 3 mm. from border of mid-region of node. This followed electrode 1 by ·025 sec..

Electrode 5. On lower end of node, followed ·005 sec. after electrode 3, and ·015 sec. after electrode 1.

Electrode 6. On right atrium, about 10 mm. from the edge of the node, followed ·030 sec. after electrode 1.

Experiment of February the 22nd (P.M.) 1913.

Five electrodes were placed in this experiment, one on the upper end of the node near its widest point (electrode 3), one on the lower portion of the node (electrode 4), two on the lower part of the superior vena cava (electrodes 1 and 2), and one on the body of the right auricle about 10 mm. from the border of the node. The initial negativity occurred in electrode 3, spread to electrodes 1 and 2 in ·005 sec. and to electrode 4 in approximately the same time. Electrode 5 (right auricle) followed in ·03 sec..

Experiment of February the 23rd, 1913.

Seven electrodes were placed in this experiment, as follows :—

Electrode 1. On auricle close to border of upper end of node.

Electrode 2. On mouth of superior vena cava, close to border of upper end of node.

Electrode 3. On sinus node, near widest portions.

Electrode 4. On auricular edge of node, 3 mm. below electrode 3.

Electrode 5. On venous edge of node, at same level as electrode 4.

Electrode 6. On lower part of node.

Electrode 7. On right atrium, 10 mm. from mid-region of node.

Negativity appeared so close together in electrodes 3, 4 and 5, all of which were on the node, that it was impossible to determine any difference in time. Electrode 2 followed in ·005 sec., electrode 7 in ·025 sec.. Satisfactory curves were not obtained from electrode 1.

Discussion of preceding experiments.

The experiments described above, concerned with negativity in the sinus node and immediately surrounding tissue, confirm the view that the nodal tissue is the first to manifest negativity. In most cases this appears first in the part of the node containing the greatest mass of tissue, usually the upper part, and spreads downwards along the node and out from the node to the surrounding tissue. The wave of negativity tends to spread up to the superior vena cava and to the venous side of the node more rapidly than to the auricular side, and regions on the venous side as compared with equidistant regions on the auricular side always show negativity first. In three of the four experiments in which comparisons were made, the negativity spread to the venous side of the node before it reached the superior vena cava. As will be evident, these, and other experiments to be reported in this paper, indicate a resistance to the spread of the wave to the auricle greater than to other regions, and the possible significance of this will be discussed later. The spread to the venous tissue from the node is rapid and the negativity may reach the mouth of the superior vena cava before other regions of the node are involved. This was true, for example, in the experiment of April the 3rd, 1913, described above. Here the mid-region of the node was negative after the mouth of the superior vena cava, while the upper part of the node preceded both of these in negativity. Had the former lead been taken alone, the conclusion would probably have been drawn that in this case the excitation was arising in the superior vena cava. The excitation, therefore, does not necessarily spread throughout the node before passing to other regions, but apparently spreads from any point in all directions to the surrounding tissues. The study of the intervals of the spread of negativity agrees well with the findings in the first four experiments described and shows that there is little delay in the passage of the wave anywhere except to the auricle. The wave of negativity spreads from the sinus node down the node and over the bordering venous tissue very rapidly. A difference in time between the upper and lower end of the node and between the node and contiguous venous tissue of ·01 sec. or less was obtained in all cases. The spread to the auricle quite close (2-3 mm.) to the node required, however, from ·015 to ·025 sec..

In a recent paper Erlanger[6] has objected to the interpretation of initial negativity on the surface of the heart as necessarily indicating that region in which the cardiac impulse arises, on the ground that the nodal tissue may represent a region in which sinus tissue comes especially close to the surface, or that as a result of accumulation of a relatively large mass of sinus tissue in this region, the impulse may be especially condensed here and affect the galvanometer, while other regions in which the negativity is less developed may actually represent the place of initial negativity and the true region of origin of the impulse. He calls attention to the fact that the amplitude of the electrical change associated with activity is largely dependent on the

mass of tissue reacting, and suggests that the excitation may actually start
in the so-called sinus region outside the node and spread across the node to
the auricles. Only when it becomes concentrated in its spread across the
node does it become sufficiently strong to affect the galvanometer. He states
that the sinus venosus of the frog's heart, which is relatively large, must give
at most a very small deflection of the galvanometer, since no evidence of it
is present on the curves that have been published (Straub). In previous
work we have recorded a wave due to sinus activity in the tortoise by
electrodes placed directly on the sinus[21] and even from the body tissues of
the animal.[7] In the latter paper we have discussed the question as to why
there is no separate wave on the normal electrocardiogram of mammals
indicating sinus activity, and have noted that the presence of such a wave
in the tortoise is the sole difference between the electrocardiograms of the
tortoise and the mammal. This we believe to be the expression of the fact
that in the mammal the sinus is fused with the auricle and the electrical
expression of its activity is normally fused in the electrocardiogram with the
wave arising from auricular activity. A full discussion of this with the
evidence for such a view is presented in the paper referred to. In order to
put to experimental test the possibility suggested by Erlanger that there may
be initial negativity of relatively small degree outside the area of nodal tissue,
we have in several hearts compared the node with outlying regions with the
galvanometer adjusted to much greater sensitiveness than usually employed.
Without exception the sinus node continued to manifest initial negativity
when compared to other regions. In the curves reproduced (Fig. 9), the
sensitiveness of the galvanometer was such that one millivolt gave a deflection
of 260 and 1050 millimeters ; sufficiently delicate to show clearly the sinus
wave of the tortoise heart. Furthermore we have found that the endocardial
surface covering the node manifests initial negativity to other regions lying
outside the node and in the immediate neighbourhood, both on the endo- and
epicardial surfaces.

*The transmission of the wave of negativity, arising in the sinus node, to the
auricles and to the auriculo-ventricular conducting system.*

In the previous section we have considered the evidence for the origin
of the wave of negativity in the sinus node, and its spread within the node
and to the tissues immediately contiguous with it. We will now consider
the spread to more distant regions and discuss, in the light of the experimental
facts, the probable path taken by the impulse in its passage to auricles and
ventricles. The regions, of which the investigation seemed of especial
importance in attempting to trace the normal path of the excitation wave,
are the mouth of the superior vena cava, the right atrium, the region of the
coronary sinus and the lower part of the interauricular septum within the
right auricle, comprising the region of the auriculo-ventricular or Tawara
node. In thirty-eight dogs, the relation of onset of negativity in these

different regions was determined by the first method described, and in this way data obtained which would indicate the order or sequence in which these regions received the excitation arising in the sinus node. Not all of these different regions were compared in every experiment, but sufficient data were obtained, as the following statement will show, to indicate the usual sequence. The two points compared as to initial negativity are given in each case together in brackets, and the numbers following indicate the number of times the region showed initial negativity when compared to the other.

Sinus node 32	Sinus node 36	Sinus node 24	Sinus node 38
Mouth of superior vena cava 0	Right atrium 0	Coronary sinus 0	Auriculo-ventricular node 2*
	Mouth of superior vena cava 21	Mouth of superior vena cava 22	Mouth of superior vena cava 19
	Right atrium 6	Coronary sinus 5	Auriculo-ventricular node 8
		Right atrium 12	Right atrium 5
		Coronary sinus 15	Auriculo-ventricular node 26
			Coronary sinus 2
			Auriculo-ventricular node 23

Next to the sinus node the mouth of the superior vena cava precedes other regions in a large proportion of the experiments, while the auriculo-ventricular node precedes the two remaining regions, the right atrium and the coronary sinus in a large percentage of cases. The data in reference to the relation between the right atrium and the coronary sinus is such as to lead to no definite conclusion as to the one which usually precedes. The usual sequence may be stated as follows :—

> Sinus node.
>
> Mouth of superior vena cava.
>
> Auriculo-ventricular node.
>
> Coronary sinus or right auricle.

While this expresses the usual sequence and the one which occurs in a large percentage of all cases, there may be a variation in the order, as reference to the data will show, though the sinus node always stands first. From the experiments first described

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* The condition of nodal rhythm, in which the impulse arises in the auriculo-ventricular node, may occur as a result of certain experimental procedures. These two hearts demonstrated nodal rhythm at the beginning of the experiment, a condition associated with simultaneous or nearly simultaneous contraction of auricles and ventricles. For this reason these two experiments have been excluded from the other totals and are only given in this one comparison.

in this paper it would seem that the excitation usually spreads to the venous side of the node before involving the superior vena cava.

Data as to the actual time required for the passage of the wave of negativity from the sinus node to the right auricle was obtained by the second method described, in fourteen experiments, and in seven of these the time for transmission to the auriculo-ventricular node was also satisfactorily determined. Wybauw,[27] in his studies upon the region of primary negativity in the dog's heart, found that the direction of movement in the curves obtained from leads from the sinus node and auricle quickly changed, and concluded that the wave of negativity was conducted from the sinus node to the auricle without any important delay and that nothing comparable to the slowing of conduction that occurs at the auriculo-ventricular junction is present at the sino-auricular junction. Certain considerations led us to doubt the value of measurements of conduction determined by this method. In a muscle composed of different layers and with considerable variation in the total mass of tissue in different regions, it would seem that little confidence can be placed in measurements of conduction based on change in direction of movement in the galvanometric curve. Measurements of this kind depend upon the assumption that a wave of negativity arises at a point (*a*) and is conducted to a point (*b*), in such a manner that the instant the point (*b*) is reached by the wave and not before or later than this time, the point (*b*) becomes negative when compared with (*a*). The result is a diphasic curve and the time of propagation of the wave from (*a*) to (*b*) is determined by measurement from the initial movement to the point on the curve where the movement passes the resting position to form the opposite limb of the diphasic curve. Should the condition of negativity continue to predominate for a time at (*a*) after it has reached (*b*) erroneous measurements would result. And it may be conceived that a strong condition of negativity might develop near (*b*) and cause the curve to change in direction before the negativity has actually travelled to (*b*). Considerations such as these led us to adopt a different method in investigating this problem. This method is described in detail in a preceding part of our paper. The results in reference to the rate of propagation of negativity from the sinus node to the right auricle and auriculo-ventricular node are as follows :—negativity in the mid-region of the right atrium followed the onset of negativity in the sinus node an average of ·0275 sec. in fourteen experiments. The highest figure obtained was ·04 sec., the lowest ·025 sec.. In five of seven experiments the wave of negativity reached the auriculo-ventricular node on an average of ·015 secs. before it spread to the body of the right auricle. The highest figure obtained was ·02 sec., the lowest ·005 sec.. In the remaining two experiments the time differences between these two regions were too small to determine accurately. All of these experiments were performed on dogs. Two experiments were carried out on cats and one on a rabbit, which showed approximately the same interval between the sinus node and the right auricle as in the dog. The rate of spread from the sinus node to the superior vena

cava and the venous and auricular tissues immediately surrounding the node has been given earlier in this paper.

Discussion of results.

Two new facts in relation to conduction of the excitation in the mammalian heart appear to be clearly shown by these experiments. First, that there is a certain resistance to the spread of the excitation from the sinus node to the main mass of the auricle ; evidenced both from direct measurements of the rate of conduction to this region as compared with conduction over the tissues bordering on the venous side of the node ; and by the fact that in the large majority of cases the excitation extends to relatively distant regions, such as the auriculo-ventricular node, before it reaches the main body of the atrium. The second fact which seems clear is that the excitation does not spread from the sinus node to the auricle and thence to the ventricle as is usually described, but is distributed to these regions by different paths. The auriculo-ventricular node, representing the beginning of the so-called auriculo-ventricular conducting system, received the excitation before the right atrium in thirty-one out of a total of thirty-eight experiments, while in two of the seven remaining instances negativity was manifest at approximately the same time at both points. Thus in only five of thirty-eight experiments did the excitation involve the auricle definitely before reaching the auriculo-ventricular node. These exceptions seem to indicate the possible spread of the excitation from the sinus directly to the auricle and to show that the impulse is not necessarily distributed to the right auricle through Tawara's node and its connections. Indeed the experiments do not necessarily indicate this in any case, and the sole conclusion that we feel justified in drawing at the present time is that stated above, namely, that the excitation does not normally spread to the auriculo-ventricular node and the ventricle by way of the main mass of the right auricle. It would seem probable that the facts are best explained, for the time at least, by supposing that the excitation spreads from the sinus node to the auriculo-ventricular node by some special path or paths, and passes directly to the right auricle through the sino-auricular junction, and that, for some reason, conduction is in most cases much slower to the auricle than to the auriculo-ventricular node. This may be represented provisionally in diagrammatic form as indicated :—
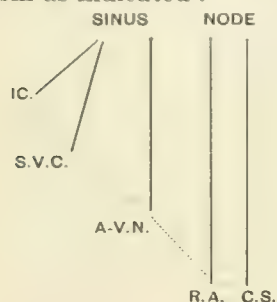
This excitation is conceived of as spreading from the sinus node to the other regions, and the relative time required for conduction over the path is indicated in each case by the length of the solid connecting line. Thus the excitation usually reaches the intercaval regions (Ic.) and the superior vena cava before any other regions, and in the great majority of cases spreads to the auriculo-ventricular node before it reaches the right auricle

or coronary sinus. That there is a direct path to these regions, not by way of the auriculo-ventricular node, is regarded as probable at present, and is represented by the direct lines connecting them with the sinus node. It is an open question as to whether the right auricle in the normally beating heart ever receives its excitation by way of the auriculo-ventricular node. Possible connections are represented by the dotted lines.

That there is an anatomical basis in the mammalian heart for the spread of the excitation from the sinus to the ventricle without passing through the auricles, is possible. The sinus in the early embryonic heart is connected with the ventricle by the auricular canal, and the auricle is a side growth from this (Keith and others). Mall[20] has recently shown that the auriculo-ventricular bundle is formed from the auricular canal and at first forms a well marked strand of tissue connecting sinus and ventricle. Thorel[26] has reported connections between the sinus and auriculo-ventricular nodes composed largely of Purkinje fibres and formed of tissue similar to that in the ramifications of the auriculo-ventricular node. This has been denied, however, by Aschoff,[1] Mönckeberg[22] and Koch.[14] Curran[4] has described in the sheep's heart examined macroscopically extensive ramifications of the auriculo-ventricular node, one of which is described as passing up in the inter-auricular septum to be lost in the auricular muscle near the mouth of the superior vena cava. Other bundles pass from the node to the main mass of musculature of the right and left auricles. Our experiments strongly suggest that such a connection may exist ; whether it is over a single well-defined path or occurs diffusely, and whether the path is composed of '' specialised '' tissue, are questions which future experimental and histological work must decide. In a recent paper Koch[14] discusses in detail the structure, connections and embryology of the sinus and auriculo-ventricular node.

It should finally be noted that the delay in passage of the excitation from the sinus node to the right auricle constitutes a definite sino-auricular interval, which according to our results, is about one-fourth the length of the auriculo-ventricular interval in the same heart. This interval evidently results from the resistance to the passage of the excitation from the node to the auricle, across the sino-auricular junction. The excitation spreads rapidly throughout the node and to contiguous venous regions, but encounters this resistance in its spread to the auricle. The nature of this resistance cannot at present be stated. It may be bound up in some way with the structure and relations of the node as a neuro-muscular organ, and possibly the delay results from passage over structures similar to the synapses of the central nervous system.

SUMMARY.

Employing the method of initial negativity in comparing two electrodes on the surface of the heart the previous work of Wybauw, and of Lewis, Oppenheimer and Oppenheimer has been confirmed, that in the dog's heart the cardiac impulse arises in a region corresponding anatomically to the

sinus node of Keith and Flack. It has been shown further that the same relations of negativity hold when the electrodes are applied to the endocardial surface of the veno-auricular regions. By determining the relations between the onset of negativity in any region and mechanical systole of the right auricle, and by comparing this relation in different regions, estimates have been made as to the rate of propagation of the wave of negativity, arising in the sinus node, to surrounding regions and to the beginning of the conducting system of the ventricle (the auriculo-ventricular node). It is shown that the wave of negativity is propagated throughout the sinus node and spreads to the contiguous venous regions with considerable rapidity, reaching the mouth of the superior vena cava in ·01 sec. or less. Its passage to the auricle is somewhat delayed, and a sino-auricular interval, averaging ·027 sec. in fourteen experiments, has been determined. This delay in passage to the auricle is such that in the great majority of the experiments the excitation spreads to the auriculo-ventricular node before involving the right atrium. This leads to the inevitable conclusion that the cardiac impulse spreads to the ventricle and to the right auricle by different paths, and does not pass to the ventricle through the auricle, as ordinarily stated. Finally, it is shown that with a galvanometer of sufficient sensitiveness to record the electric wave arising from the sinus venosus in the tortoise heart, the sinus node of the dog's heart continues to show initial negativity to all other regions. This was shown in order to meet the objection that the wave of negativity may arise outside of the sinus node and first become sufficiently concentrated in this region to affect the galvanometer with the instrument of the sensitiveness usually employed.

The above statements are derived from a total of thirty-eight experiments on dogs' hearts beating *in situ.*

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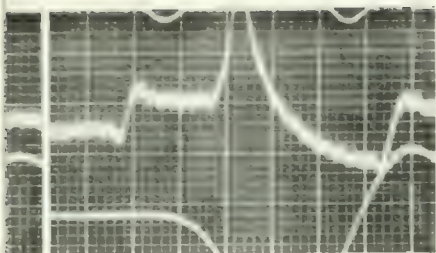
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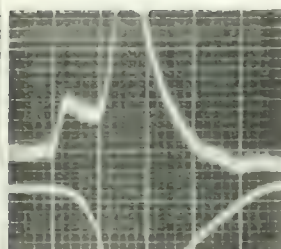
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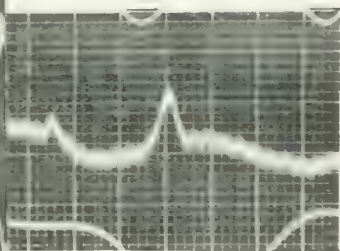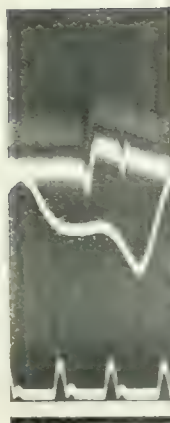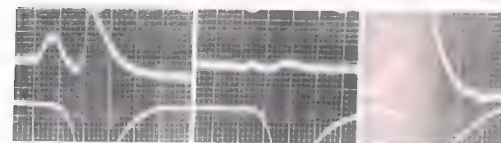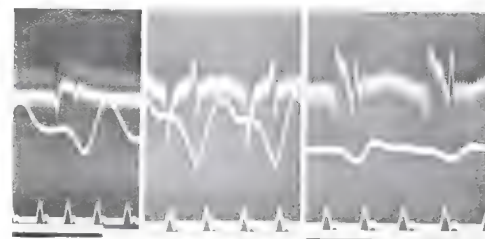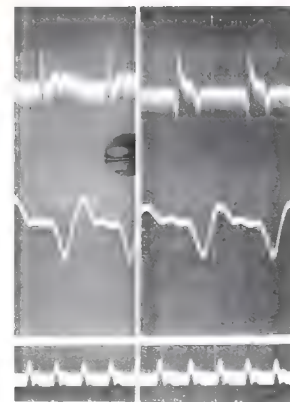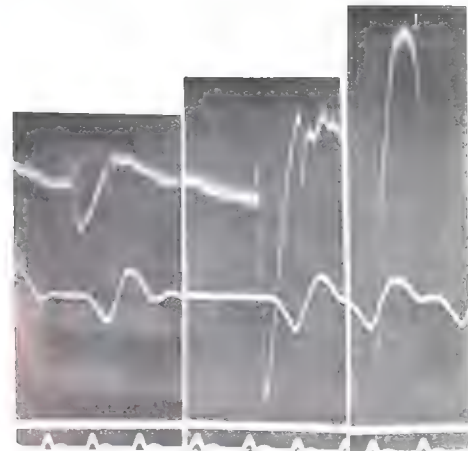
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EXPERIMENTS ON THE ORIGIN AND PROPAGATION OF THE IMPULSE IN THE HEART.

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OBSERVATIONS ON DYING MAMMALIAN HEARTS.

Introduction.

A NUMBER of workers have attempted to determine the region of the mammalian heart which retains its power of contraction longest in the dying heart (*ultimum moriens*), on the assumption that that region which is normally most rhythmic and which, therefore, acts as pacemaker for the normal heart will be the last to survive. The divergent results that have been obtained by different workers using this method, as well as certain theoretical considerations which will be discussed later, led us to test this method by comparing the results obtained from inspection of the dying heart with those obtained by direct determination of the region in which the excitation arose by the method of initial electric negativity.

Historical data.

The fact that the venous and auricular regions of the heart usually retain their power of contraction in the dying organ after the ventricles have ceased to beat, was known to the older physiologists, and mention is made of this in the writings of Harvey, Haller and Nysten. Attempts to localise the ultimum moriens more exactly have been made by a number of physiologists in modern times. MacWilliams[14] and Hering[7] found the region of the mouth of the vena cava to manifest contraction after all other regions had become quiescent, while Fredericq[5] placed the ultimum moriens in a region somewhat lower down between the two venæ cavæ. In a few cases Hering found the region of the mouth of the inferior vena cava to show contractions after all other supraventricular parts had ceased to contract. In a later paper Hering[8] states that those cases in which the ultimum moriens is apparently in the inferior cava, the beat really originates in the region of the auriculo-ventricular node at the base of the interauricular septum. He finds that the most frequent seat of the last noticeable contractions is over a region along the sulcus terminalis, corresponding to the position of the sinus node of Keith and Flack.[10] Koch[11] examined the dying hearts of four still-born human fœtuses and found that the last region to show contraction was the mouth of the coronary sinus, and concluded that his findings lent support to the view put forward by Tawara, on his discovery of the auriculo-ventricular node, namely, that it is this region which represents the principal cardio-motor centre. Koch cut away from these hearts various parts of the supraventricular regions, including the superior vena cava, atrium and appendage of the right auricle, and parts of the

interauricular septum, and observed the effects on the rate of contraction of the ventricles. No effect occurred until the lower third of the interauricular septum, and the region around the mouth of the coronary vein was removed, when the ventricular beat ceased. Koch[12] more recently, while accepting as probable the origin of the impulse in the normal heart as higher up than the coronary sinus, nevertheless affirms his earlier observations that the region of the coronary sinus is the last to show contraction in dying hearts. Hirschfelder and Eyster.[9] in observing the dying hearts of dogs and cats, were impressed with the relative infrequency of definite contractions in the mouths of the great veins and the general complete dissociations between such contractions, when present, and the contractions of other parts of the auricles. Erlanger and Blackman[3] were unable to make a finer localisation of the ultimum moriens than the region of the great veins as a whole.

Methods.

The hearts were exposed *in situ* with the animals under artificial respiration and ether anæsthesia. The artificial respiration was stopped and the animals allowed to become asphyxiated. The region including the mouths of the superior and inferior vena cava, the intercaval regions, the atrium, and the right auricular appendage, were carefully watched in the dying heart and any visible beat noted. When a region showed conspicuous movement after all other regions had ceased to move or were contracting less strongly, this was compared with other regions as to initial negativity by connecting to the string galvanometer and recording the curve on photographic paper. The normal birthplace of the excitation was determined by the usual procedure (see Part I) before asphyxia was allowed to develop.

Results.

Four experiments were performed, two on cats, one on a dog and one on a rabbit. The protocols of these are given below :—

Experiment of February the 8th, 1912. Cat.

In the normal beat the region of the sinus node precedes the mouth of the superior vena cava in negativity by ·012 seconds and the right atrium by ·025 seconds. Asphyxia allowed to develop. Auricular appendage continued to beat feebly after rest of supraventricular regions became quiescent. Later, regions around the base of the right auricle and along sulcus terminalis showed visible contractions. These regions were formerly entirely quiescent. Finally, weak contractions developed at the mouth of the superior vena cava, and involved about five millimeters of the lower end of the vein. The beat was, as near as could be determined, simultaneous throughout the regions involved. Ventricle quiescent except occasional weak beat. Atrium had ceased beating. Galvanometric curves at this time showed that the first region to show negativity was the mouth of the superior vena cava, and this was followed by the region along the sulcus terminalis (sinus node) and this, in turn, by the right atrium.

The regions in the dying heart in which the powers of contraction survived longest thus comprised the mouth of the superior vena cava and the tissue along the sulcus terminalis. The galvanometric curves showed that the excitation was arising in the former region, while in the naturally beating heart the reverse was true.

Experiment of February the 9th, 1912. Dog.

In the normal heart initial negativity was present in the upper part of the sinus node, and spread to the lower end of the node and surrounding regions, involving the superior vena cava in ·015 seconds and the right atrium in ·025 seconds. In the dying heart, as a result of asphyxia and for a considerable period, the only beat noted was in the right auricular appendage. Later a beat became evident in the basal portions of the right auricle and gradually increased in strength. No visible contraction was present either in the mouth of the superior vena cava or along the sulcus terminalis comprising the region of the sinus node. The galvanometric curves showed, however,

that the sinus node, which showed no contraction, was negative before the superior vena cava and the region of the right atrium which was showing well developed contractions. The excitation was thus arising in a region which showed no visible contraction (sinus node region) and spreading to involve a region in which contractions were well developed (basal parts of right auricle).

Experiment of February the 10th, 1912. Cat.

Negativity began in upper part of sinus node region in the normal heart, spread to lower end of sulcus and to mouth of superior vena cava in ·01 and to right atrium in ·025 seconds. In asphyxiated heart contractions developed in basal parts of the right atrium, the sulcus terminalis and the mouth of the superior vena cava. The contraction appeared definitely to originate in the superior vena cava and to spread, in the form of a wave, to involve the sulcus and basal parts of auricle. There was no distinct interruption in the wave during its passage to these regions. Galvanometric curves taken at this time showed that the sulcus region was negative before the mouth of the superior vena cava and the right auricle.

In this heart the excitation in the dying organ was thus arising in the same region as in the normal (sinus node region), a part which, however, appeared to contract after a neighbouring region (mouth of superior vena cava).

Experiment of February the 27th, 1912. Rabbit.

In the normal heart the upper part of the sulcus terminalis was negative before the superior vena cava and right auricle (time intervals not determined). This relation continued in the dying heart at a time when the sole region showing any evidence of contraction was the lower end of the superior vena cava. This is an example of the excitation apparently originating in a region showing no visible contraction and spreading to a region, the seat of well developed contractions.

Discussion.

It is evident from the experiments reported that the two methods employed, inspection and the electrical method, frequently give contradictory results as to the region in which the excitation arises in hearts dying from asphyxiation. Furthermore, the impulse may arise in the dying heart in a region different from that in which it arose in the same heart beating under more normal conditions. It would seem that of all methods which have been employed to determine the seat of origin of the normal cardiac impulse, the one which depends upon the determination of the ultimum moriens is most likely to lead to erroneous conclusions. The divergent conclusions arrived at by different workers using this method is, therefore, not surprising. As Erlanger[2] has pointed out, the logic of this method of determining the normal seat of impulse initiation is not entirely clear, since it serves only to locate the most viable parts of the heart and not necessarily those which possess normally the highest degree of automaticity. In our experience a region which frequently shows the strongest and at times the sole power of contraction in the dying heart is the right auricular appendage, a region in which rhythmicity is normally absent or at least very slightly developed (Erlanger,[1] Langendorff[13]).

Another point brought out by these experiments, to which we wish to call attention, is that the excitation may arise, in certain cases, in regions of the dying heart which show no visible contraction. A part therefore, which is not beating, or in which the contractions are too small to be seen or recorded, may be the seat of impulse formation. This suggests a possible differentiation of the properties of automaticity and contractility in certain regions of the heart. Whether such differentiation is absolute or relative, would seem to depend upon the question as to whether muscle may contract without the contraction being visible, a possibility maintained by some writers. As to this, we have no evidence from our experiments, and indeed it is difficult to see how direct experimental evidence can be obtained to

throw light on this assumption. Our results merely show that impulse initiation (automaticity) may be present to almost normal extent (as judged by the rate of impulse formation) in regions in which contractility is greatly reduced or possibly absent. The work of Gaskell, MacWilliams, Englemann, Erlanger and others has shown that the different properties of heart muscle are present in different degrees relative to each other in different parts of the heart. Erlanger[1] and Fredericq[6] have shown for example that the left auricle in the mammalian heart does not as a rule manifest automaticity, while contractility and the other properties of cardiac muscle are well developed.* It is but a step further to the view that in other regions, in which automaticity is well developed, that this development has occurred at the expense of other properties, especially contractility, and that in the most automatic regions contractility is normally greatly reduced or absent. This view has been expressed by one of us[4] previously to account for the absence of a wave on the venous pulse curve that could be referred to contraction of the sinus region of the mammalian heart. It seems significant to us in this connection that, in our experience, any contraction which may be seen in the dying heart along the sulcus terminalis and involving the region of the sinus node, to which most of the known facts point as the normal seat of origin of the cardiac impulse, develops gradually in force and reaches a maximum during the course of observation, and is usually totally absent for a period of time after the heart has become sufficiently slowed to detect it if present.

Summary.

Observations were made on the ultimum moriens of the dying mammalian heart which lead to the conclusion that the last portion retaining the power of contraction is not necessarily indicative of the seat of normal impulse formation. It is furthermore shown that excitations may arise in regions of cardiac tissue showing no visible contraction, and it is suggested that contractility may be normally much reduced or dormant in that region in which automaticity is most developed and in which normally the cardiac impulse arises.

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* For discussion as to the probability of complete differentiation between the processes of conduction and contraction in heart muscle see Hoffmann (Archiv. f. d. ges. Physiol., 1910, cxxxiii, 552), and Eyster and Meek (Archiv. of internal Med., 1913, xi, 204).

THE OCCURRENCE OF AURICULAR CONTRACTIONS IN A CASE OF INCOMPLETE AND COMPLETE HEART-BLOCK DUE TO STIMULI RECEIVED FROM THE CONTRACTING VENTRICLES.

By ALFRED E. COHN and FRANCIS R. FRASER.

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In a patient sixty-two years of age, probably suffering from syphilis, we were able to demonstrate the presence of incomplete auriculo-ventricular heart-block (Fig. 1). During a long period of observation we noticed a frequent change from incomplete block to complete auriculo-ventricular dissociation. We were able to satisfy ourselves that the change in the heart's rhythm depended in great part on the fluctuation in the rate of the auricles in the same way as has been reported by Erlanger[5] in a patient and by Erlanger and Hirschfelder[6] in experiments. During the periods when the rhythm was one of complete dissociation, we noticed that the ventricles were often followed by small waves easily distinguished in the electrocardiograms. These we have identified as the representatives of auricular contractions resulting from stimuli received from the contracting ventricles. It is the occurrence of these waves and certain facts related to them that we wish to report.

Apart from auricular contractions, which occurred normally in this patient, an abnormal form also appeared. The abnormal complexes were found only after independent ventricular contractions, never after sequential cycles, the interval between ventricular and auricular representatives being 0·1 to 0·14 seconds. The conduction time of stimuli passing in the normal direction was most often 0·2 seconds, though sometimes it was slightly less. In the electrocardiograms (Fig. 2, 3, 5 and 6), these waves are represented by small acute (1 to 1·5 mm.) deflections directed downwards. They are obviously auricular contractions and result from ventricular beats which stimulate the auricles to contraction. A single wave of the kind described is seen in Fig. 2. The time at which it appears is just before a normal (sinus) auricular contraction is expected. It is the only point in the curve where the regularly recurring upright auricular complex fails to appear. In its place is an auricular beat represented by a negative wave of the kind described. In all the curves which were taken from this patient, these inverted waves appeared only shortly before the normal (upright) ones were expected; that is to say, they appeared only in the late, but never in the early portion

of the diastoles of normal auricular contractions. If both a normal and a sequential auricular contraction became due during the period of late diastole, then the normal beat invariably occurred and the abnormal one was suppressed (* in Fig. 3).

A comparison of Fig. 4 and 5 illustrates these points. In Fig. 4 no auricular beats follow the contractions of the ventricles. Of the three ventricular complexes shown, the first and third are preceded by normal auricular beats, but none is seen in relation with the second. An auricular contraction is due and must indeed have occurred at the same time as the middle ventricular beat, for this R wave is 2 to 3 mm. taller than the other two. The normal auricular beats occurred then in close proximity to the three ventricular systoles, and stimuli to which the contractions of the ventricles gave rise reached the auricles when they were refractory. In Fig. 5 the interval between the normal (upright) auricular representations is equal to two of those seen in Fig. 4. If the remaining ones were present, they would fall a little more than 0·2 seconds after the beginning of the ventricular complexes; that is to say, auricular diastole would terminate 0·2 seconds after the beginning of ventricular systoles. But before this length of time has elapsed, stimuli from the ventricles have reached the auricles and have occasioned contractions which are represented by negative P waves. Such waves appear after each of the ventricular complexes in Fig. 5. They have forestalled the normal auricular beats and have taken their places.

Auricular contractions of similar form and similarly situated were observed experimentally by one of us.* In dogs morphine was injected intravenously, on the plan of v. Egmond[3] and of Einthoven and Wieringa,[4] to stimulate the cardio-inhibitory mechanism. Under these circumstances the rate of the auricles is reduced so that it is sometimes slower than that usually developed inherently by the ventricles. Instances in which the auricular rate was only 11 per minute were observed. The independent ventricular contractions which arose often occasioned stimuli which caused auricular contractions like those seen in this patient. An instance where the auricular beats of the variety under discussion appeared, when the rate of the normal auricular contractions was very slow, is seen in Fig. 6, taken from our patient, where the reduction in the auricular rate was due to vagus pressure.

Discussion.

In connection with the occurrence of auricular contractions as the result of stimuli arising in the ventricles, several matters of interest deserve consideration. The first relates to the form of the electrocardiographic waves. In our patient and also in the experimental curves to which we have referred, the auricular curves are downwardly directed deflections. Lewis[8]

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* A report dealing with this subject appears in the Journal of Experimental Medicine, 1913, xviii, 715.

showed in his experiments that waves of this outline usually resulted when the stimulus to contraction spread from a focus situated at the lower levels of the auricular muscle. More recently, Ganter and Zahn[7] have attempted to show in a preliminary publication that, if the auricular contraction is represented by an inverted wave, the stimulus to contraction arises in the auricular portion of the auriculo-ventricular node—a portion identical with that described by one of us[1] as the auriculo-nodal junction. In general, experimentors are agreed that when contractions spread from the lower part of the auricular musculature, the wave in the electrocardiogram is likely to be inverted. In our own case the contractions seem to have spread in the same way, but did so in response to stimuli which arose in the walls of the ventricles.

We have stated that unless the ventricular stimuli occurred late in the normal auricular diastoles, no abnormal auricular contractions resulted. In Fig. 3 it is quite clear that an abnormal beat failed to appear at a point 0·37 seconds (P-R = 0·24 plus R-P in this curve = 0·13 seconds) after the preceding normal auricular contraction. In the same curve, a negative P wave did occur 0·6 seconds after a normal P, so the refractory period of the auricle is certainly less than this length of time (0·6 seconds). Although we know that the refractory period is at least 0·37 seconds, our curves do not permit us to state exactly how much longer it is. Its length lies between 0·37 and 0·6 seconds. Another point suggested by Fig. 2 must be considered. The last interauricular interval reproduced measures 0·75 seconds and it ends 0·27 seconds after the beginning of the preceding R wave. According to the other examples, a negative P wave was expected 0·13 seconds before this time had elapsed. A satisfactory explanation for its absence cannot be given. But we have already shown an instance (* in Fig. 3) where a normal beat and an abnormal one are due simultaneously, and the normal one prevails. Here, as elsewhere in these curves, the normal beat not only prevails when both are expected together, but frequently also when the abnormal beat falls in what may be called its presystolic period. But that this is not always the case is seen in Fig. 5, where the retrograde beats appear, though normal ones are due directly afterwards. It is possible that the question of the auricular rate, as Trendelenburg[10] has shown, so different in the two examples reproduced, may have an influence upon the occurrence of one or other type.

The failure of the auricles to respond to the stimuli from the ventricles early in diastole may be attributed to one of two causes. The irritability of the auricular muscle may not have recovered to a sufficient degree for it to respond to a stimulus of the strength supplied by the contraction of the ventricles. Or, stated in another way, the auricles remain refractory to normal stimuli for longer periods than are observed in experimental conditions. The refractory period has, in fact, been shown by Trendelenburg[9] to be somewhat longer in the auricles than in the ventricles, but these results were obtained from experiments upon frogs' hearts, and the

results apply to electrical stimuli.   Experiments more nearly approximating the normal conditions in mammal or in human hearts are unknown to us. We must conclude that contractions resulting from physiological stimuli can occur only in a much later portion of auricular diastole than is the case when artificial excitations are employed.

Although the abnormal auricular beats which we have described follow invariably on ventricular beats which immediately precede them, we have not ventured to describe them as being retrograde in the sense that the stimuli arising in the ventricular walls passed in the reverse direction over the auriculo-ventricular bundle.   It is their occurrence in a case of heart-block which has made us hesitate to give them this designation, even though we know that the bundle was capable of conducting impulses in this patient. For records from another patient* have since come to our notice, in which similar waves appeared, and this patient during four or more years of constant observation has invariably been the subject of complete heart-block. A consideration of the curves from this patient induces us to consider the possibility that the abnormal auricular beats in both patients were due to the mechanical stimulus of the contracting ventricular mass acting upon the auricular tissues.

SUMMARY.

We have described, in a case of heart-block which was sometimes complete and sometimes incomplete, the occurrence of auricular contractions due to stimuli received from the contracting ventricles, while auricles and ventricles were beating in complete dissociation.   The case belongs to a group in which the rhythm of the heart depended in large measure on the rate of the auricles.

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* These records were shown to one of us (A. E. C.) by Dr. John Parkinson and were taken by him from one of Dr. James Mackenzie's patients at the London Hospital.   Dr. Parkinson will describe this case later.

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Fig. 1.   Leads *I*, *II* and *III*.   Incomplete heart-block (2 : 1).

Fig. 2.   Lead *II*.   A single retrograde (ventricular) auricular systole and a single co-ordinated cycle is seen in a stretch of curve otherwise showing complete dissociation.

Fig. 3.   Lead *II*.   Taken during an atropine test   The figure shows complete dissociation. One auricular systole is due to a retrograde (ventricular) stimulus.

Fig. 4.   Lead *II*.   Taken during digitalis intoxication.   Complete dissociation is shown.

Fig. 5.   Lead *II*.   Taken during digitalis intoxication.   The figure shows complete dissociation. Auricular contractions due to retrograde (ventricular) stimuli are seen.

Fig. 6.   Lead *III*.   The arrows indicate the onset and offset of pressure over the right vagus nerve.

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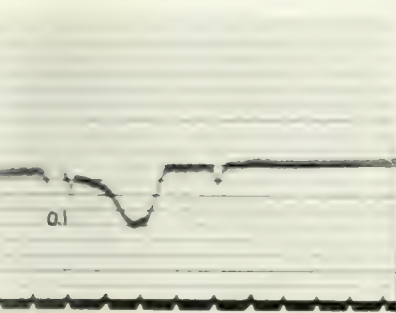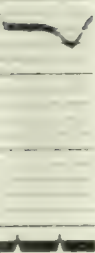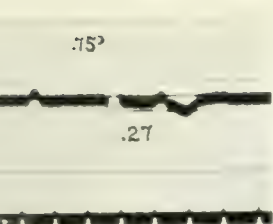
Fig. 6.
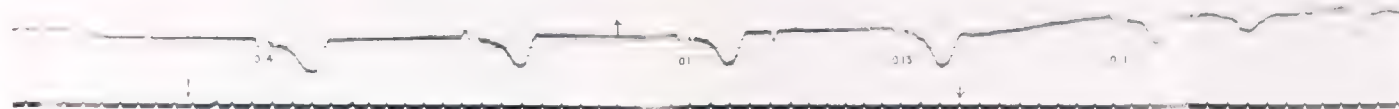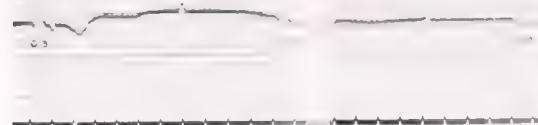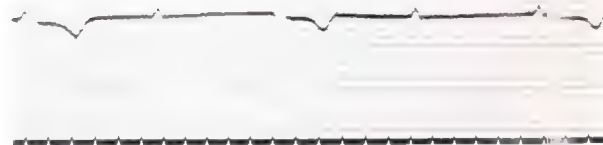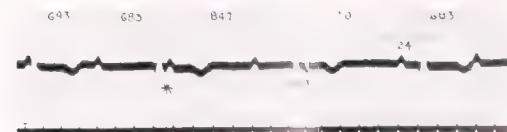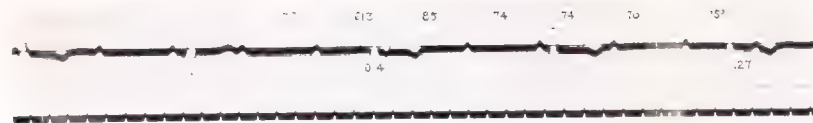
A CASE OF HEART-BLOCK IN WHICH THERE WAS NO PATHOLOGICAL LESION OF THE CONNECTING MUSCULAR SYSTEM.

By W. E. HUME.
(*Newcastle.*)

THE relationship between clinical auriculo-ventricular dissociation and a pathological lesion of the auriculo-ventricular bundle has been established in many instances. Pathologically, gummatous, sclerotic, and calcareous changes have been found in the auriculo-ventricular node and bundle and in many cases the muscular connection between auricles and ventricles has been completely severed. In some instances, however, the damage has been less complete and partial lesions have been described, such as a " tendency to sclerosis."

On the other hand, there are at least three cases of heart-block on record in which no demonstrable lesion could be found in the auriculo-ventricular node and bundle.

Fahr.[1] describing three cases of complete auriculo-ventricular dissociation, found definite lesions in two of them ; in one case a tumour completely infiltrated the bundle, and in the other the right and left limbs of the bundle were invaded by fibrous tissue. In a third case no lesion was found in that portion of the node and bundle which was examined ; the bifurcation of the bundle and its two branches were not examined, as this region was not included in the block of tissue taken for microscopical examination. Fahr attributes this omission to the abnormal length of the bundle.

In Krumbhaar's case,[2] a diffuse fibrotic change was found in the ventricular muscle, but the auriculo-ventricular bundle and its ramifications appeared to be quite normal. Krumbhaar suggested that in this instance the heart-block might be associated in some way with fibrosis of the sino-auricular node. Ivy Mackenzie points out that this suggestion must be accepted with some reserve, as a fibrotic condition of the node is a common occurrence in hearts which have presented no clinical abnormality. Price and Ivy Mackenzie[3] have recorded an instance of complete heart-block with auricular fibrillation in a child suffering from diphtheria. In this heart no structural abnormality was discovered in the conducting system. They suggest that the impairment of conductivity might be due to lesions in the ventricular fibres themselves which rendered them incapable of responding to auricular impulses.

The present case exhibited all the phenomena associated with the Stokes-Adams syndrome. During life there was auricular fibrillation and heart-block, combined with short periods of unconsciousness. On a microscopic examination of the heart the auriculo-ventricular node and bundle and the two main branches were found to be perfectly normal. Certain of the Purkinje fibres were found to be degenerated.

Clinical history. H. N., aged 69, a labourer, was admitted under my care in the Royal Victoria Infirmary, Newcastle-on-Tyne, on July the 18th, 1912. For some nine-ten months prior to admission the patient had suffered from shortness of breath on exertion, being embarrassed by walking quite short distances (10 yards). For the last five months he had suffered from attacks of giddiness which at times caused him to fall and rendered him unconscious. These attacks sometimes occurred six-seven times in the day. He was warned of their onset by a sharp shooting pain on the left side of the face and head which spread over the forehead ; he felt giddy and fell rigid with arms and legs extended. After a minute or two he regained consciousness, and was able to rise without assistance. He had recently experienced some precordial pain and tenderness in the left breast.

Up to one month before admission he had acted as watchman for the corporation. He was able to sit at his door and guard the corporation property on the road, which was undergoing repairs, at the front of his house.

Family and previous history. His father died at the age of 61 from alcoholism. His mother died at the age of 50 of heart disease. He has three brothers, and of three sisters two are quite healthy. One sister is said to suffer from heart disease. There was no history of tuberculosis or cancer in the family. The patient stated that he had been a perfectly healthy man until ten months ago, when the present illness started. For 40 years he was a sea-going stoker-engineer, and for the last 8 years had done odd labouring work. He had partaken moderately of alcohol (chiefly beer). He smoked about three ounces of tobacco a week.

He denied, and there was no evidence of, any venereal disease.

Condition on admission. Patient was a thin spare man who weighed eight stones, his original weight being ten stones. He was short of breath, and had to be propped up in bed on account of dyspnœa. He had a constant bronchitic cough. The tongue was clean, and he had a fair appetite. The radial artery was markedly thickened, and the maximum blood pressure was found to be 230 mm. of mercury (Riva Rocci). The pulse was slow, being counted at the wrist at 32 beats per minute. The force was good. The temporal and brachial arteries were similarly thickened.

The apex of the heart lay in the fifth interspace four inches from the nipple line, and was localised and forcible. The area of cardiac dulness extended from the fourth rib above and the left sternal border to the apex. On auscultation there was a first sound and a blowing systolic murmur, which was conducted a hand's breadth towards the axilla. The aortic second sound was accentuated. There were signs of emphysema and rhonchi were to be heard throughout both lungs. There was no œdema of the extremities. There was a commencing cataract in the left eye, though no other abnormality could be detected in the special sense organs. The nervous system was normal. The liver dulness was not increased. Fifty ounces of urine were passed per diem. The specific gravity was 1,018. There was no albumen nor sugar.

Course of illness. While he lay at rest in bed there were no fits, though the patient occasionally complained of giddiness. The pulse never varied more than 4 beats in the minute, being always counted at 32-36. He slept badly and was very breathless. His cough was constant and wearisome.

On July the 21*st*, the pulse was 30 per minute, and the patient complained of feeling very giddy at times though he never lost consciousness.

On July the 25*th*, at 6.15 a.m. he managed to partake of breakfast, and about a quarter of an hour after he had finished, the breathing became very difficult and the face was noticed to be cyanosed. There was considerable rattling in the throat and chest. Breathing ceased and artificial respiration was resorted to. During this apnœic period the pulse was imperceptible at the wrist. After artificial respiration had been done for three or four minutes normal breathing returned. Then it was found that the pulse was fast and feeble. The breathing, on recovery, was laboured and rapid. For

three-quarters of an hour periods of apnœa and dyspnœa alternated. The pulse always re-appeared at the wrist before the re-establishment of physiological breathing. During one period of apnœa neither the pulse nor respirations returned, and the patient died.

Polygraphic tracings. Polygraphic tracings were taken on each day from July the 12th to the 24th; their characteristics were always the same, and are represented in Fig. 1. In this figure it will be seen that the pulse periods are always regular and each measures two seconds.
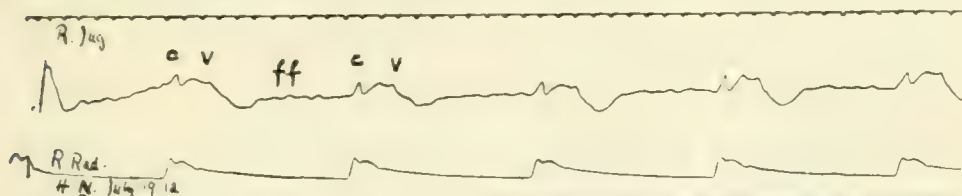
Fig. 1. Jugular and radial curves. In the jugular curve fine waves ff. indicative of auricular fibrillation are seen.

In the jugular curve the whole of the diastolic period is occupied by fine waves indicative of auricular fibrillation. There is no evidence of a single a wave.

On July the 21st, one-fiftieth grain of atropine sulphate was administered hypodermically. This injection had no effect at all on the pulse rate. There was, however, some parching of the mouth and dilatation of the right pupil.

Pathological examination.

This was made on the day of death, before the onset of rigor mortis. On opening the thorax there was a considerable quantity of clear fluid in both pleural cavities. Both lungs were collapsed and congested. Throughout the bronchial ramifications there was a large quantity of tough muco-pus. There were signs of old healed tuberculosis in both lungs, and in the bronchial glands.

The liver and spleen showed changes characteristic of passive congestion. The kidneys were normal in size; on section the capsule stripped with difficulty, and the surface of the kidneys was pitted and showed numerous cysts. The cortex was narrowed. The vessels were thickened and prominent. There was a small fibroma in one of the pyramids of the left kidney. Chronic venous congestion was marked in both organs.

The whole heart was enlarged and there was a considerable increase of sub-pericardial fat which was especially noticeable on the surface of the right side of the heart. The right auricle and appendix were slightly dilated and the walls hypertrophied. The tricuspid orifice admitted the tips of four fingers; the valve was not abnormally thickened. The right ventricle was slightly dilated and the wall was infiltrated with fat especially towards the apex. The muscle of the right ventricle was of a brown colour suggestive of brown atrophy. The pulmonary valve was normal. The left auricle

and appendix were hypertrophied and dilated. The endocardium of the left ventricle was thickened. The ventricular wall at the level of the attachment of the papillary muscle measured 2 cms. in thickness. The muscle was firm and did not give the appearance of excessive fibrosis. The mitral valve was normal. There was some degeneration at the bases of the aortic cusps but the edges of the valves were thin and membraneous. There was considerable thickening of the intima of the aorta, and a few small isolated opaque patches of atheroma. The coronary arteries were both considerably thickened, the thickening being due to a proliferation of the intima. Throughout the distribution of the coronary vessels there were small yellow patches of atheroma.

Microscopic examination of the heart. The heart was forwarded to Professor Keith, Royal College of Surgeons, for microscopic examination, and I am much obliged to him for sections, and for his opinion on their appearances.

1. The region of the sino-auricular node was embedded in paraffin and cut at right angles to its long axis. The fibres of the node were well formed and there was no evidence of fibrosis or leucocytic infiltration.

2. The fibres of the auriculo-ventricular node were well formed though scanty in number. The bundle was triangular in shape, the sections being cut in the plane of the long axis of the heart, and was separated from the surrounding muscle fibres by a capsule of fibrous tissue. The muscle fibres of the bundle were well formed and there was a complete absence of any increase of fibrous tissue in their midst.

3. The bundle was followed into right and left branches which likewise appeared to be normal. The terminations of the branches amongst the ventricular muscle fibres stained poorly and appeared to be degenerated. Professor Keith remarked on this degenerated appearance of the Purkinje cells. He stated " that he was afraid to make any definite or dogmatic statement on this point, because in hearts which he had reason to believe were normal he had seen similar appearances."

4. Pieces of auricular and ventricular muscle were examined, and in places some chronic interstitial fibrosis was discovered.

Conclusion.

A consideration of this case and of similar cases in the literature makes it evident that our knowledge of the etiology of clinical heart-block is incomplete. It would appear that functional as well as organic impairment of the auriculo-ventricular node and bundle may be responsible for the blocking of impulses from auricles to ventricles.

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[3] Price and Mackenzie.   *Heart*, 1911-12, iii, 233.

THE ESTIMATION OF DIASTOLIC BLOOD-PRESSURE IN MAN.

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THE importance of a knowledge of the diastolic pressure need hardly be emphasised, bearing in mind the valuable indications it may afford as to the peripheral resistance, the help it may give in interpreting the conditions of the circulation through its relation to the systolic pressure (pulse-pressure range), and the significance of its direct influence on the arterial walls (as the continuous distending force which they bear) and on the aortic valves.

Little attention is at present given to diastolic pressure in view of the prevailing opinion that there is no reliable and practicable method of ascertaining it, existing methods being difficult of application and uncertain as regards interpretation. Even as regards normal men diverse values have been stated as standards of diastolic pressure by different observers, and similar diversity of opinion naturally results as to the actual range of pulse-pressure in different conditions.

PART I.

THE MAXIMUM OSCILLATION METHOD.

Before entering on the consideration of the maximum oscillation method, some other plans which have been proposed may be briefly referred to. Masing[19] made sphygmograms from the artery distally to the armlet, and took the armlet pressure at which the maximum excursion of the sphygmographic lever occurred as the indication of diastolic pressure. Strassburger's[27] method is to raise the pressure in the armlet gradually and determine by palpation of the artery below when the pulse begins to feel smaller. Ehret[4] used a similar plan. Sahli[25] and Bingel[1] based their estimations on graphic records from the artery distally to the armlet. Observations on the foregoing plans have been made by many observers.

But in these methods the changes taken as indicating diastolic pressure are difficult of determination and interpretation. It is true that there are decided pressure changes in the artery distally to the armlet when the pressure in the latter is gradually raised or lowered. In our experiments such

changes, as indicated manometrically, did not usually coincide with the internal diastolic pressure, but occurred while the external pressure was at higher levels ; there was considerable variation in the precise relation of such changes to the actual diastolic pressure. These points are stated later in this paper. (See pages 163 & 164.)

The chief forms of apparatus used for the study of maximum pulsation are those in which pressure is applied to a limb by means of an armlet which is connected with an indicator of some kind. The latter may be arranged to yield visual indications, the magnitude of the oscillations being judged by the eye, as in Hill and Barnard's[11] larger apparatus, the compressed-air manometer of Oliver,[21] the oscillometer of Pachon,[22] and the mercury manometers of Stanton's[26] and of Janeway's[13] apparatus, &c., these latter being applications of Gumprecht's[10] observations that the oscillations of the Riva Rocci apparatus could be used for this purpose. Or, graphic records may be obtained by Gibson's[8] apparatus with Singer's modification, by Recklinghausen's[23] apparatus, and by the well-known Erlanger[5] sphygmomanometer.

The simpler forms in which pressure was applied locally over an artery as in von Basch's apparatus, Hill and Barnard's pocket sphygmometer, Oliver's hæmadynamometer, &c., have now been superseded by the above-mentioned types.

Views as to the significance of maximum oscillation.

As to the interpretation of the data provided by the maximum oscillation method there has been wide diversity of opinion.

Marey[17] introduced a new criterion for the estimation of blood-pressure by ascertaining the external pressure at which maximum pulsation occurs ; he enunciated the principle, commonly designated by his name, that when the pulsations become maximal the pressure outside the artery must equal that within the vessel.

This principle of estimation, characterised by Janeway as unquestionably our most exact indirect measure of a blood-pressure, was applied by Mosso[19] in his sphygmomanometer ; the latter investigator offered experimental proof of the theoretical accuracy of the method. He experimented with two vessels communicating by an opening closed by an unstretched elastic membrane. But such conditions differ widely from those present in the arteries used for blood-pressure estimations in man. Mosso believed that it was the mean pressure that he estimated by his sphygmomanometer.

Roy and Adami[24] concluded that the pulse-wave, as tested by their experimental sphygmometer, attained its maximum size when the extra-vascular pressure reached a height which just exceeded the minimum intra-vascular pressure. These observers applied local pressure to the radial artery by a small bag filled with water, a method now known to be attended by many sources of fallacy.

Hill and Barnard thought that the instruments devised by them indicated the mean pressure, and were confirmed in this opinion by experimentally testing a dog's thigh with an armlet and a pocket sphygmometer, the indications of the latter as regards maximum oscillation being compared with the readings of a mercury manometer connected with a cannula in the other femoral artery. They obtained corresponding values.

C. J. Martin[18] confirmed this experimental finding as to the relation of maximum oscillation to mean blood-pressure. He found that Hill and Barnard's small sphygmometer and Oliver's hæmadynamometer gave sufficiently accurate indications of mean pressure when applied to a length of exposed artery lying on a flat resistant surface, but not under conditions more nearly comparable to those present in the human subject. With the armlet also, even when filled with water, connected with a mercury manometer, he obtained dubious and variable results. Martin expresses a strong opinion " that the maximum systolic is the only point in the varying pressures of the cardiac cycle which can be determined with any degree of accuracy without opening an artery."

Sahli[25] regarded maximum oscillation as an indication of diastolic pressure, while Tschlenoff[28] associated it with systolic pressure.

Howell and Brush[12] fixed diastolic pressure as the phase of intra-arterial pressure to which maximum oscillation corresponds, at least under experimental conditions with an exposed artery subjected to circular compression. They enclosed a carotid artery (dog) in a glass tube and used valved manometers to show the intra-arterial pressure in the other carotid, &c. The artery examined was closed distally by being tied or connected to a manometer.

Howell and Brush's result is in accordance with Marey's principle, and it has been the accepted view since their investigation that maximum oscillation indicates diastolic pressure; this conclusion has been applied in the large amount of clinical work that has been done on the subject with the various forms of apparatus used, such as those of Erlanger, Oliver, Janeway, Gibson, Pachon, and Recklinghausen—the two last named being largely employed on the continent.

At the same time it is noteworthy that there has been so marked a conflict of evidence obtained by skilled observers (Hill, Martin, Howell and others) in regard to the manometric verification of the indications afforded by maximum oscillation—as to whether it is the mean or the diastolic arterial pressure that is indicated.

Oliver, who had for some years regarded maximum oscillation as indicating diastolic pressure, has recently inclined to the view that mean pressure may be the one indicated.

Mackenzie[15] believes that there is no definite point in the series of oscillations obtained with rising and falling external pressures that can be taken as an indication of diastolic pressure.

The diastolic index.

With the forms of apparatus in which the maximum of the oscillation has to be judged by the eye difficulty has been very generally felt in determining the optimum excursion, and anything like a precise definition of this is indeed very often impossible as the oscillations may look maximal over a considerable range of the external pressure which the instrument exerts upon the artery.

The same holds good when a graphic record is obtained, not only when air is used as the transmitting medium to the Hg. manometer, as in the instruments of Erlanger and Gibson, but even when the armlet and the connecting tube to the manometer are filled with water, as was done by Martin whose tracings show practically maximal oscillation over a considerable range of pressure with the oscillation magnitude tailing off above and below. Martin recommends (for estimating the *mean* pressure) raising the external pressure till it is certain that the oscillations diminish and recording this point, then lowering the external pressure till an undoubted diminution takes place; the mean between these two points to be taken. Gibson also recommends the taking of the middle point in the period of maximum oscillation, which is commonly an extended one in the tracings yielded by his apparatus; this is to meet or minimise a source of fallacy depending on the inertia of the mercury, as suggested long ago by Marey. While the pressure in the armlet is being continuously lowered (method of continuous escapement) the falling mercury carries the lowest point of maximum oscillation in the manometer down too far; hence Gibson prefers the middle point to the actual lowest point of maximum oscillation.

Recklinghausen, on the other hand, associated the lowest point at which the oscillation is maximal with the minimal intra-arterial pressure, *i.e.*, just before the abrupt diminution in the size of the oscillations which he found to occur as soon as the extra-vascular pressure fell below the diastolic pressure within the artery.

Erlanger interprets the tracings got with his sphygmomanometer by taking the point of maximal oscillation or the lowest point at which the oscillation is maximal (Recklinghausen's index) as a measure of the diastolic pressure. He states that when proper precautions are observed these two points usually coincide. But in the experience of many observers this point is often not at all definite, and opinions may differ markedly as to the precise point to be selected. On submitting tracings taken by this method to different observers, we have often found much diversity in regard to the point chosen, and in many cases great difficulty in deciding upon any point at all. In other cases the sudden diminution is quite well marked and affords very definite and valuable indications.

PRELIMINARY EXPERIMENTS.

Before proceeding to investigate the conditions and significance of maximal oscillation by means of a circulatory schema, we experimented on arteries to determine (1) the behaviour of their walls when compressed by definite increments of external pressure, and (2) the effects on the arterial volume of definite rises of internal pressure acting on arteries that are under the influence of different amounts of external pressure. Arteries being tubes of very special structure and properties, it is essential to use these in the living state, tested in different conditions; experiments with rubber tubes, &c., are on a different footing altogether.

Behaviour of the arterial tube when subjected to external pressures.

The behaviour of the arterial tube under the influence of external pressure was tested by placing a portion of artery in a plethysmograph or compression tube filled with oxygenated Ringer's fluid, in which the external pressure (*i.e.*, the pressure on the external surface of the artery) could be increased at will, the amount of such pressure being indicated by a mercury manometer. One end of the artery was closed by its being tied on a glass or wooden rod which passed through one of the rubber corks of the compression tube ; the other end was connected with a long horizontal tube of small calibre passing through the other cork. The artery was filled at zero pressure with Ringer's fluid which also extended for a short distance along the horizontal tube. Raising the external pressure gradually compressed the artery ; the resulting displacement of fluid from its interior was read off on a millimetre scale placed alongside the horizontal tube. The plethysmograph and its contents were kept at approximately body temperature. The pressure was raised by increments that varied in different experiments, and at intervals of different duration—commonly 1 minute periods.

The results obtained varied according to the increments of pressure used as a test. (With *small* increments compressibility and distensibility differ.)

When rises of 5-10 mm. Hg. are employed, contracted and relaxed arteries show remarkable differences in behaviour. In the former the displacements are at first small, gradually increasing to a maximum and then declining.* (Fig. 1.) In the relaxed vessel the first rise of external pressure causes the maximum effect—followed by diminishing effects on the cubic capacity of the tube. (Fig. 2.) These effects strikingly resemble the changes in capacity produced by similar increments of internal pressure in contracted and relaxed arteries respectively, as described by one of us (J. A. MacW.) many years ago. With certain tests the compressibility of the vessels seems to be closely comparable to their distensibility, at least as far as the broad features of their behaviour are concerned ; the processes of compression from without and distension from within show notable similarity in their development.

But such increments of external pressure as 5-10 mm. Hg., while quite suitable for contracted arteries presenting considerable resistance to flattening, are much too large to serve as an accurate test for relaxed arteries, the first increment being sufficient to flatten the vessel along almost its whole length without affording an opportunity for the behaviour of the tube at the different phases to be analysed. Consequently we have tried very small rises of pressure measured by a water-manometer, *e.g.*, 10-20 mm. H_2O. With such small increments a very different picture is obtained—a gradual increase in the changes of cubic capacity up to a maximum, followed by a declining

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* The final phases approaching complete obliteration when the displacements become extremely small are not to be regarded as accurately indicating changes in the tube as a whole. For at this stage the changes are chiefly near the ends kept open where tied on the glass tube or rod, when the rest of the artery has become obliterated.

series, *i.e.*, a behaviour similar in character to what occurs with a contracted artery, differing only in regard to the pressures required. (Fig. 13.)

Similar features are evident when an india-rubber tube is tested in the same way, large increments of external pressure being used in this (resistant) tube. (Fig. 4.) Such features are evidently common to tubes in general.

It is clear that the resistance of the tube (artery, &c.) is relatively high to begin with, when the circular form of the tube has to be distorted, and
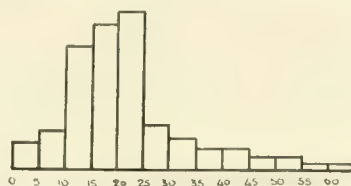
Fig. 1. Contracted artery. Volume changes caused by 5 mm. Hg. increments of external pressure.
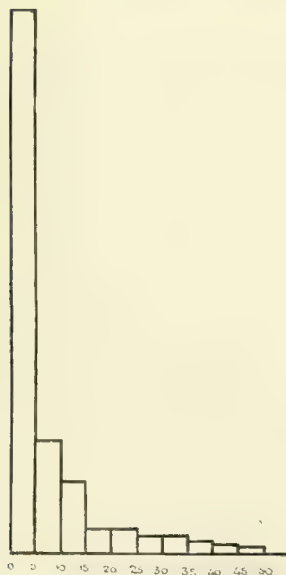
Fig. 3. Relaxed artery. Volume changes caused by 10 mm. H_2O increments of external pressure.

Fig. 2. Relaxed artery. Volume changes caused by 5 mm. Hg. increments of external pressure.
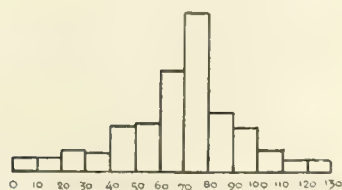
Fig. 4. Rubber tube. Volume changes caused by 10 mm. Hg. increments of external pressure.

that the maximum effect from equal increase of external pressure is got when the tube has reached an oval or half-flattened form. Small alterations of external pressure in this region would obviously give the greatest effect in the way of volume change.

Similarly, in the intact circulation changes in the veins from the oval to the circular form can readily provide a large increase in the capacity of the venous system with comparatively little alteration of internal pressure.

Volume changes caused by rises of internal pressure.

In this paper the term "zero position" is used to mean that of an artery in the normal circular form with zero pressure in its interior, *i.e.*, undistended. By "half-flattening" is meant such an approximate amount of flattening as is present when the shorter diameter is roughly about one-half that of the tube in its circular form. In "complete flattening" the sides of the vessels are opposed to one another with more or less complete obliteration of the lumen. (Fig. 5.)

We have compared the efficacy of changes of internal pressure acting on the arterial tube in the above-mentioned three positions and also when distended to various extents beyond the zero position.
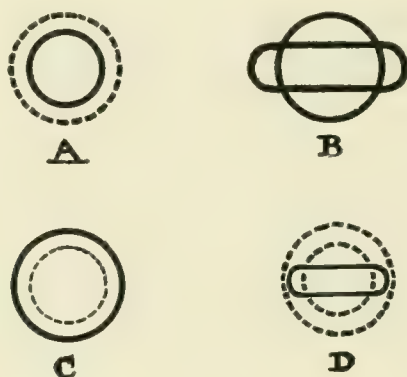
Fig. 5.

A.   The continuous circle represents the zero position, and the broken line the diastolic position, the artery being expanded to a considerable (though variable) extent by the diastolic pressure within it.

B.   The zero and the half-flattened positions are shown.

C.   The continuous line represents the artery distended by diastolic pressure ; the broken line (zero) position to which the vessel returns when the internal diastolic pressure is counterbalanced by the application of external pressure.

D.   The outer and inner circles (broken lines) indicate the diastolic and zero positions respectively ; the continuous line indicates the half-flattened position. In the phase of maximal oscillation the arterial tube changes from the half-flattened into the diastolic position, and then becomes further expanded to a variable extent by the systolic rise of pressure.

We began with such small alterations of internal or external pressure as are necessary to change an artery from the circular to the half-flattened position or *vice versa*. With an artery in the compression tube in the usual way we measured the amount of fluid displaced from it when half-flattening was caused by raising the external pressure to a sufficient extent. The artery was, to begin with, filled with fluid at zero pressure ; one of the tubes leading from it was closed, while the other communicated with a horizontal glass tube of small calibre fitted with a millimetre scale. The displacement of fluid from the interior of the artery was measured by its

movement along the horizontal tube. With a relaxed or slightly contracted artery (*e.g.*, carotid of sheep) a very small pressure sufficed to cause half-flattening and a considerable volume change. Taking off the external pressure of course caused a return to the circular form with the same volume change ; the same result followed a similar small rise of internal pressure— to counterbalance the external pressure which had caused half-flattening.

In this way the amount of pressure necessary to change the vessel from the half-flattened to the circular form and the volume change resulting therefrom were ascertained.

The effects of such small alterations in pressure were then tested by experiments in which the same rise of internal pressure from zero or from various levels above zero was induced. The change in the external volume of the artery was determined by using the compression tube as a plethysmograph, one of the branches of its side tube being closed and the other connected to a horizontal glass tube with a scale. The expansion caused by a certain rise of internal pressure was read off on this scale. As the pressure alterations involved were small in the case of such an artery as the relaxed carotid of the sheep (*e.g.*, 2 mm. Hg. or less) a water-manometer was used to measure them.

In this way it is easy to compare the changes in arterial volume caused by a certain small rise of internal pressure acting on the artery (*a*) in the half-flattened and (*b*) in the zero position, or (*c*) at various phases of distension beyond the latter position. Even in a relaxed and highly distensible artery the volume change is found to be much greater in (*a*) than in (*b*) and very much greater than in (*c*). In other words the effectiveness of a small rise of internal pressure is very much greater when starting with a half-flattened artery than when acting on one in the circular form at zero pressure. In a normal relaxed artery the completely flattened position is not nearly so favourable to start from as the half-flattened state. The small rise of pressure acts much more effectively on (*a*) than on (*b*), the volume change being often three or more times as great in the former as in the latter. In such comparisons exactly equal periods of time must be allowed before reading the results, as the expansion and recovery of an artery with rises and falls of pressure are processes requiring a considerable time for their completion, the after-extension, &c., of such tissues being important. The results are of course strictly relative.

The actual pulse pressure in the circulation is, however, very much greater than those small rises ; the amount needed to open up the half-flattened artery forms only a small part of the pulse-pressure. Hence the essential comparison is between the effect of a few mm. of pressure expended (*a*) in changing the tube from the half-flattened to the circular position, and (*b*) the effect of a similar rise of pressure in carrying out the last part of the expansion of the circular tube in the systolic phase beyond the zero position. Are the few mm. more effectively spent in doing (*a*) and so not being available for (*b*), the amount available for distending the tube from

the zero position being the pulse-pressure *minus* the few mm. in question ? Is the pulse-pressure more effective when starting from the half-flattened or the zero (circular) position ?

Assuming the pulse-pressure to be 40 mm. and 5 mm. to be necessary to open up the half-flattened vessel to the circular form in the time available, there will be 35 mm. available for distension from the zero position. In the other case, starting from the zero position the whole 40 mm. will act on the circular tube. Are the 5 mm. more effective in the former case than in the latter, when serving as the final increment in distending the circular tube ? The more the artery is distended—assuming it to be a relaxed or a slightly contracted one—before the final increment of internal pressure comes into action, the less effect it will have since it becomes less distensible at high pressures, the co-efficiency of elasticity increasing greatly.

A strongly contracted artery would yield more *relatively* at higher increments but the *actual* change would be very small, in the brief time that the pressure rise acts. Such transient rises have little effect in expanding a strongly-contracted artery ; the process of expansion goes on slowly and a considerable time is necessary for the manifestation of anything approaching the full effect which a certain increment of pressure may be capable of exercising upon the arterial wall.

We tried the effects of systolic rises of values resembling those of the pulse-pressure in the circulation, starting from (*a*) the half-flattened position, and (*b*) the zero position, &c. The former position (*a*) is established by the pressure of a column of fluid of sufficient height, this fluid being contained in a tube connecting the side-piece of the compression tube with the horizontal measuring tube, which in this case was placed on a level elevated to a suitable extent. Such experiments were made with arteries in various conditions, with results that were always of the same nature, the advantage as regards the magnitude of the volume oscillation always being associated with (*a*). This holds good even when with an extremely distensile artery which expands extensively both transversely and longitudinally when starting from the zero position (*b*). An extreme case of such an artery was obtained by using an ox carotid which had been softened by exposure to ammonia vapour for some minutes. With an internal rise of 30 mm. the expansions in (*a*) and (*b*) bore the ratio of about 130 : 80 ; with a rise of 70 mm. such ratio as 35 : 23, &c., the volume change from the half-flattened position being thus about half as great again as from the zero position, even with so abnormally distensible a vessel. With less distensibility a still greater advantage rests with (*a*).

All the foregoing experiments give results which concur in showing that in such distensible tubes as normal arteries, relaxed or in a state of moderate tone, the half-flattened position is the optimum one for a systolic expansion to start from. In relatively non-distensible vessels, whether strongly contracted or pathologically altered, a greater degree of flattening is found to be advantageous.

The pressure changes tested in these experiments are of considerable duration (1 min., &c.). The results are indicative of important differences in the behaviour of the arteries in various conditions, and the presumption is that a broad similarity of behaviour must be manifested in the different time relations that are present in the human circulation. To obtain further evidence, experiments with pressures varying at rates comparable to those in the circulation were carried out by means of a schema.

Using a compression tube of the type already described, we placed in it a length (10-14 cm.) of contracted or relaxed artery, tied on glass tubes of similar calibre which passed through the rubber corks of the compression tube. Valved manometers (maximum and minimum) were connected near the proximal and distal ends of the compression tube, connections of equal calibre and length being used. Spring outlets were employed to regulate the peripheral resistance. Ringer's fluid was used as the perfusing fluid, and the same filled the space around the artery and the tubes leading to the manometers. The general arrangement is indicated in Fig. 6.
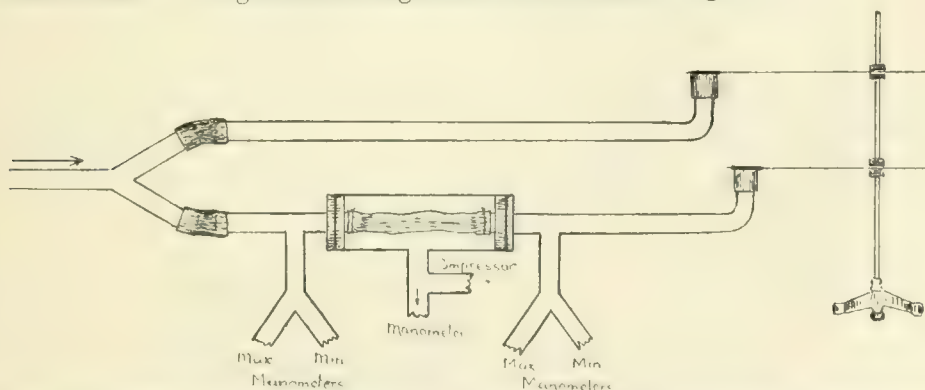
Fig. 6. Arrangement for studying maximum oscillation in an excised artery. The proximal and distal pairs of manometers (maximal and minimal) are connected near to and at equal distances from the ends of the artery in the compression tube. The side tube of the compression tube or plethysmograph communicates with a Fick manometer or other recording apparatus, as well as with an Oliver's screw compressor. Tested separately the Fick manometer gave, with pressures up to at least 160 mm., practically equal excursions in response to equal increments of internal pressure.

The external pressure around the artery in the compression tube was raised by a compressor, usually Oliver's screw compressor ; connected by a T piece with the same branch of the side tube of the compression tube was a mercury manometer to indicate the height of the internal pressure. The other branch of the side tube led to a Fick manometer, used to record the oscillations of the arterial volume. When tracings were being taken the compressor was shut off by a stop-cock between it and the compression tube ; a stop-cock between the latter and the Hg. manometer was turned just enough to allow the pressure changes to show in the Hg. manometer while not cutting down the oscillations in the Fick much. This stop-cock when once arranged was left unchanged during a series of observations.

By this method graphic records of oscillation were got, with measurements of the internal pressure (systolic and diastolic) on both the proximal and the distal aspects of the artery under examination, while the vessel itself was studied by direct inspection and the changes apparent in it were correlated with the variations in the oscillation, the internal pressures, the relation of the latter to the external pressure around the artery, &c.

In a number of experiments the Erlanger recording apparatus was used, being connected with the compression tube instead of the Fick manometer; air was commonly used as the transmitting medium in these experiments. The main results were essentially similar to those obtained with the Fick manometer, though there were some differences in detail.

To establish the relation of maximum oscillation to internal pressure is by no means a simple matter in an experimental schema.

Some investigators have used an ordinary Hg. manometer and have drawn conclusions as to the relations of the external pressure (at which maximum oscillation occurs) and the internal diastolic and systolic pressures, evidently overlooking the serious nature of the errors that may arise from the use of a simple Hg. manometer for this purpose—errors varying not only in amount but in their nature, under the influence of different rates of pulsation, &c.

Martin measured the internal pressure in his experimental schema by an ordinary recording Hg. manometer. Erlanger used a maximum and minimum manometer placed on the proximal side of the tube, &c., under examination; on the distal side he used in some experiments a mercury manometer to record the pulsations passing through.

The existence of constrictions at any part of the channel has to be carefully guarded against. We tie glass tubes of uniform calibre into the arteries, not cannulas with constricted necks. Torsion of the artery and disturbance of the arterial tube that may result from ligaturing branches too close to their origin have also to be avoided. Leaks in the vessel have been tested for by air pressure.

The external pressures are inscribed above the tracings, with the exception of Fig. 17. The internal pressures are marked below the tracings, those on the proximal side, systolic and diastolic, as Prox. $\{^{S.}_{D.}$; those on the distal side as Dist. $\{^{S.}_{D.}$

Measurement of internal pressure. It is necessary to obtain readings of systolic and diastolic pressures both proximally and distally to the artery in the compression tube, adjusting the valved manometers with each alteration of the external pressure. There may under some conditions be a considerable pressure gradient in the stream between the proximal and the distal manometers; in such a case the actual pressure within the artery is decidedly different from what is indicated by the proximal manometers. The artery may show flattening when subjected to an external pressure lower than the reading of the proximal minimal manometer, in which case there

is obviously a fall of pressure between the proximal manometer connection and the artery ; this fall is shown by the lower reading in the distal manometer. If a steep gradient is present, the pressure varies considerably along the length of the artery, so that there is a definite external pressure acting on the whole of an artery which has differences of internal pressure at different parts of its course. We have usually arranged our schema so as to have comparatively slight pressure differences between the proximal and distal

Fig. 7. The tracing is to be read from left to right. This artery had a strongly resistant wall. There is marked difference in the effects of a falling and a rising external pressure. The maximal phase is much above the actual diastolic pressure within the artery. The phase (90 mm.) of relatively small oscillation adjoining one of approximately maximal size, there being an abrupt change from one to the other, is nearer the diastolic pressure. The external pressures are marked above the tracing, the internal pressures below. The prox. systolic (S.) is immediately below the tracing, then the prox. diastolic (D.). Lower down come the distal systolic and the distal diastolic.
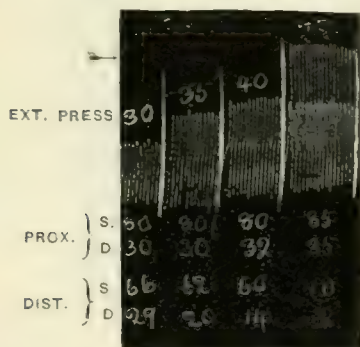
Fig. 8. Carotid, ox. With an external pressure equal to the internal diastolic the oscillation is relatively small. The maximal phase is not reached till the external pressure (45 mm.) is much above the internal. There is a marked fall in the distal diastolic at 35 mm. external pressure, very considerably before the maximal oscillation.

ends of the artery. The ends of the artery being equidistant from the manometer connections the actual pressure at the middle of the artery is obtained by taking the mean of the proximal and distal pressures. But considerable disturbances in the internal pressures and the relations of the proximal and distal pressures may be caused by the application of external pressure ; this is especially marked in regard to the distal pressures at a certain level upon gradual elevation of the external pressure. Up to a

certain height there is little or no change in the distal pressures ; then the latter become lowered very much, the diastolic pressure being extensively affected at an earlier phase than the systolic. The relation of distal to proximal pressures becomes greatly changed. (See Fig. 7, 8, 9, 11.)
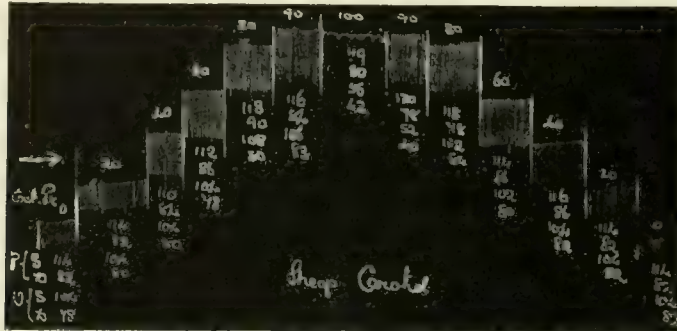
Fig. 9. The tracing reads from left to right. Relaxed artery. The oscillation shows a gradual change in size at different external pressures. The fall in distal diastolic pressure occurs at an external pressure higher than is necessary to elicit the maximum oscillation, and at different levels with a rising and with a falling external pressure.
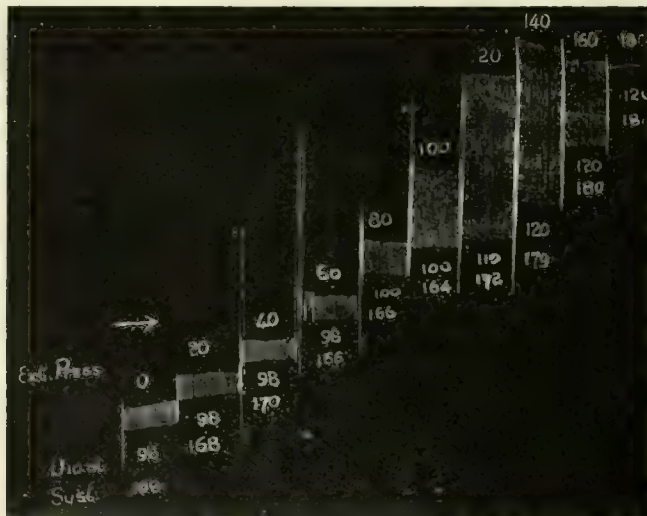
Fig. 10. Carotid, ox. The maximal phase is above the diastolic [pressure indicated by the proximal manometer. The preceding phase corresponds to the proximal diastolic pressure (100 mm.) ; there is an abrupt change in size between this and the maximal phase. There is also an abrupt change between 100 and 80 external pressure.
The distal pressures are not recorded in this tracing.

After such disturbance has occurred the actual pressures present in the artery cannot with confidence be deduced from a comparison of the proximal and distal pressures ; the mean between these two cannot safely be taken as indicating the pressure in the artery midway between the proximal and

distal manometer connections. The relation of the occurrence of an extensive change of this sort to the phase of maximal volume oscillations varies. (1) The change is commonly established when the external pressure is raised sufficiently to induce the phase of maximum oscillation, though differences in this, as in other respects, may be seen in the same artery with rising and with falling external pressure. (See Fig. 7, 11.) (2) Sometimes the disturbance in the distal pressures begins and becomes well marked much lower than the phase of maximum oscillation (Fig. 8), corresponding pretty closely, it may be, with the internal diastolic pressure as indicated by the proximal manometer. (3) In other experiments (Fig. 9, 12, 13), no marked disturbance occurred until the external pressure had been raised to a point decidedly above the phase of maximum oscillation.*

We find that the changes in the internal pressures caused by the application of external pressure vary strikingly, according as the latter is applied (1) while the stream is flowing through the artery in the usual way, and (2) while the stream is stopped by clamping the tube beyond the connection of the distal manometers.†

In (1) the proximal pressures, both systolic and diastolic, usually tend to rise more or less distinctly though the change is not usually an extensive one ; above a certain level of external pressure the distal pressures, systolic and diastolic, fall very markedly, the diastolic being often extensively affected at an earlier stage than the systolic. (See Figs.)

In (2) the systolic pressures, proximal and distal, are lowered while the diastolic pressures, proximal and distal, become elevated. (Fig. 14.)

The foregoing effects of external pressure are of course most marked when a large artery (*e.g.*, carotid of ox, &c.), is tested.

The effects of external pressure upon the internal pressure are influenced to some extent according as to whether the air in the compression tube is, or is not, in continuity with the air in the Oliver's compressor, rubber bag, &c., used for raising the pressure. While continuity is present the effects are appreciably more extensive ; when the reservoir of air in the compressor is shut off there are notable differences in effect according as to whether it is shut off during the systolic or the diastolic phase, the influence of the latter approaching nearer to that present during continuity, *i.e.*, diminution of systolic and increase of diastolic pressures.

Turning off and on the Hg. manometer used to measure external pressure is in certain circumstances not free from some disturbing influence on the internal pressures.

In regard to the comparison of the size of the oscillations at different external pressures it is, of course, essential to record the exact amount of the pulse-pressure at each phase, varying to some extent as it may do under different conditions. Through the influence of a temporary increase of the range between the systolic and diastolic pressures (pulse-pressure) it is clear that oscillations of disproportionately large size might be got at a phase other than the optimum position of the arterial wall.

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* The variation in the relation of these changes to the actual pressures throws grave doubt on the reliability of the various methods, based on the recognition of such changes, which have been proposed by different workers for the estimation of the diastolic pressure in man.

† In their experiments on animals Howell and Brush closed the artery (carotid) which they examined in their plethysmograph, by ligaturing it peripherally or connecting it to a manometer.
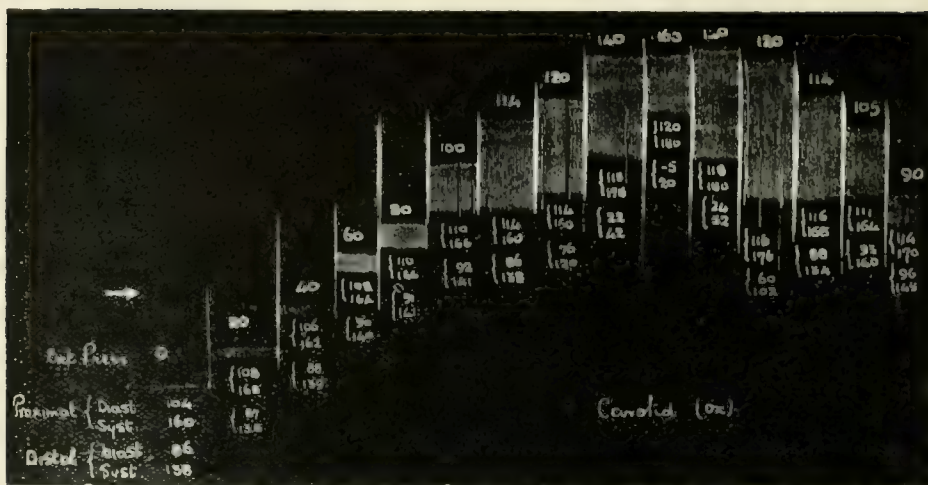
Fig. 11. The behaviour of the oscillation is different with the rise and fall of the external pressure, the size being greater during the fall and the maximum phase at 120 instead of 140 mm. external pressure. It is difficult to say which phase should be taken to represent the Recklinghausen index ; there is no definite indication corresponding to the internal diastolic pressure.
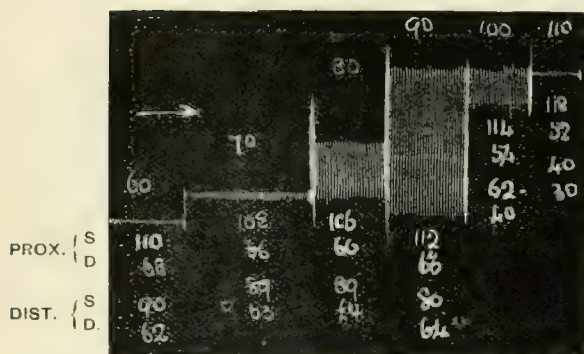
Fig. 12. Carotid, sheep (natural size). The phase of maximum oscillation (90 mm. external pressure),is much above the internal diastolic pressure. The preceding phase of much smaller oscillation is also at an external pressure (80 mm.) much too high.
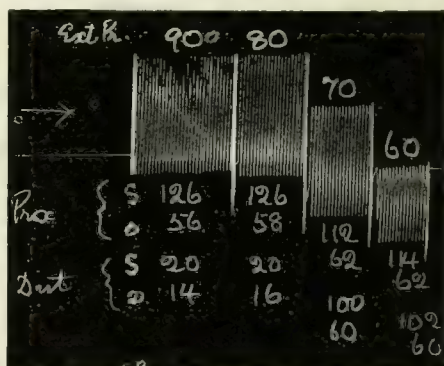
Fig. 13. Carotid, ox. Maximal oscillation occurs considerably above the internal diastolic pressure. The external pressure (60 mm.) immediately after the abrupt diminution from the approximately maximal size corresponds pretty closely with the internal diastolic pressure.
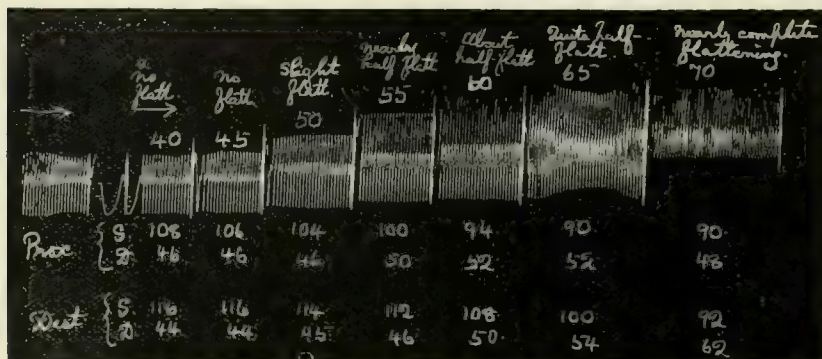
Fig. 14. Carotid, ox. The general relations of flattening to oscillation magnitude and internal pressures are shown in this tracing. It is to be noted that there was no stream flowing through the artery in this experiment, a clamp having been applied on the distal side—beyond the distal manometer connection. Application of external pressure leads to a fall of systolic and a rise of diastolic pressures, both proximally and distally.

Measurement of external pressure.

In comparing the extravascular and intravascular pressures and their relation to the development of volume oscillations the mode of measuring the external pressure is necessarily important. Is it the mean pressure or the minimum between the pulse beats that is to be taken? The latter is obviously the one that directly influences the size of the artery between the systoles — in the diastolic phase. With large pulse-pressures and a distensible artery pretty large variations in the external pressure occur at each pulse-beat, as seen clinically from the oscillations of the mercury in the apparatus of Janeway, Stanton, Gibson and others. Mean and minimal pressures must evidently have notably different values.

Erlanger in some experiments compared the measurements of external pressure in his plethysmograph—apparently with air transmission—by an ordinary Hg. manometer, and a minimum manometer; he obtained practically corresponding readings from the two, and he seems to interpret the readings as indicating minimum pressure.

With our circulatory scheme we have compared simultaneous readings by the Hg. manometer (compensated) and the valued minimum manometer under two conditions (1) with the space around the artery and in the tubes leading to the manometers filled with air, and (2) with Ringer's fluid replacing the air. Quite different results were yielded in the two cases. In (1) the minimum manometer gave lower readings than the mean of the ordinary Hg. manometer, but the differences were slight except when the volume oscillation was very extensive, the differences being more marked with the higher external pressures, and being trivial at atmospheric pressure when the air served as a highly compressible medium. For example, when the Hg. manometer showed a mean pressure of 58 mm. the minimum manometer reading was 50; when the former stood at 32 mm. the latter was 30 mm.

It is to be noted that a *mean* external pressure exactly equal to the internal diastolic pressure would not bring the artery to the zero position between the beats; a *diastolic* external pressure equal to the internal is necessary.

In (2) with an incompressible transmitting medium the movements in the Hg. manometer, when uncompensated, were of very considerable extent, varying of course with the pulse-pressure, and the size and distensibility of the artery. The minimum manometer gave a much lower reading than before, much below the mean pressure indicated by the compensated Hg. manometer, the discrepancy often being a very important one. When uncompensated the lowest point in the movement of the free-swinging mercury commonly did not coincide with the reading of the minimum manometer on account of the inertia error of the Hg. giving too low a value with a slow pulse and too high with a quick pulse.

RELATION OF EXTERNAL AND INTERNAL PRESSURES DURING MAXIMAL OSCILLATION.

In view of the complexity of the conditions affecting the volume oscillations, as stated later, it is not surprising to find very considerable diversity in the results. Much depends on what is taken as the measure of diastolic internal pressure—the pressure on the proximal side of the artery or the average between the proximal and the distal pressures. In regard to the latter the great disturbance which occurs with a certain elevation of the external pressures introduces great difficulty in determining the actual pressure in the artery lying between the proximal and distal manometer connections. Under such complex conditions as may be present here, we have not felt warranted in taking the average between the proximal and distal readings as indicating the true pressure in the interior of the artery. We have relied rather on experiments in which the disturbance referred to had not occurred on raising the external pressure sufficiently to elicit maximal oscillation and where the differences between the proximal and distal readings were small, the pressure gradient being a slight one.

We find that the diastolic external pressure necessary to elicit maximal oscillation is always higher than the actual diastolic pressure within the artery; the difference is increased if the mean external pressure is taken for

comparison. The excess of external pressure varies greatly, from a few mm. Hg. to 20 mm. or more ; it often amounts to about 10 mm.. (See Fig. 10-16.)

If the average between the proximal and distal pressures were used in the cases where a great fall in the distal pressure has been caused by the application of external pressure, the discrepancy between the external and internal pressures during the phase of maximal oscillation would of course be much greater.

The position of the maximal phase and the magnitude of the oscillations may vary with a falling as compared with a rising external pressure.   (Fig. 7 and 11.)

When an abrupt change is evident in the decline of the oscillation magnitude from the large or merely maximal size such is commonly associated with an approximate equality of external and internal pressures, such equality being present when the external pressure has been lowered just sufficiently to give the characteristic reduction in oscillation magnitude which is often-times easily recognisable.

Condition of the artery during maximum oscillation.

Normal distensible artery.   Direct observation of relaxed normal artery in the compression tube, while the external pressure around the vessel is being gradually raised or lowered and its pulsatory oscillations in volume are being graphically recorded, makes it very plain that the maximum oscillations do not occur (as is believed at present) when the external pressure is such as to cause the vessel to return to the condition of the passive artery (empty, or filled with blood at zero pressure) between the pulse beats.   The present view, in accordance with Marey's principle, is that the volume change is greatest when the expansion starts from the condition of the "passive" artery, the circular unstretched tube being then ready to undergo the greatest enlargement during the systolic rise of internal pressure—the change being from a circular tube of smaller size to one of larger size. (Fig. 5A.)

Direct inspection shows that this view is not correct.   The conditions just described do not by any means give the largest oscillations.   When the external pressure is further raised, so as to cause an alteration in the form of the tube in the diastolic intervals, a certain amount of flattening or distortion from the circular form, a decided increase in the magnitude of the volume oscillations is seen.   Maximal oscillation does not develop until flattening reaches such a degree that the shorter diameter of the tube is (roughly) something like half that of the passive circular tube—a condition to which, for convenience, we have applied the term " half-flattening."* (Fig. 5B.)

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* A similar condition is probably present in a normal artery when a sphygmograph is applied and the maximum excursion of the lever is being obtained.   That the vessel is by no means completely flattened between the beats is indicated by the fact that when the brachial artery is closed by digital pressure the sphygmograph lever sinks markedly.

When the external pressure is carried so high as to cause complete or nearly complete flattening of the artery between the pulse beats the oscillations are markedly diminished, the optimum point being decidedly exceeded.

When the external pressure is first raised to the obliteration point and then gradually lowered, a series of similar changes, in inverse order, is evident.

Nature of the volume changes in maximum oscillation.

We have found that this differs in two conditions :—

(1) In the normal distensible artery ;

(2) In non-distensible tubes ; and in arteries that are practically or relatively non-distensible at blood-pressure, on account of the presence of strong contraction or of pathological change.

Normal distensible artery. The volume increase represented by each oscillation is compounded of two portions :—

(a) The volume change caused by an alteration from the half-flattened to the circular form (zero position). (Fig. 5, B and D.)

(b) Expansion of the circular tube from the zero position towards or beyond the diastolic position, i.e., the position of the arterial wall in diastole when the diastolic pressure is not counterbalanced by external pressure. According to the view at present accepted (b) is the only factor in the production of the oscillation. (Fig. 5, A and D.)

In the normal state when no external pressure is applied to an artery, its expansion at each pulse-beat is relatively slight, on account of the fact that the vessel is already very considerably distended by the permanent diastolic pressure and not easily distended very much more by the systolic rise.* It follows that if the artery is reduced to the zero position by counterbalancing the internal diastolic pressure by external pressure, the systolic pulse pressure would then, acting on the undistended tube, produce much more expansion than when it acts on an artery already distended to the diastolic size. This difference is one that would naturally be predicated in the case of a relaxed artery, from what is known as to the diminishing increments of volume caused by successive increments of internal pressure. In a contracted artery, on the other hand, the distensibility has been found to be greater at a phase when the vessel is already filled at considerable pressure—the amount varying according to the strength of contraction present. But this difference in a contracted artery is only relative, and the actual amount of distension (at any phase) induced by such quick and transient rises of pressure as those of the pulse waves is very slight ; this has

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* Changes in length, straightening of curves and locomotion are commonly much more marked than transverse expansion.

been shown by direct experiment by one of us (J. A. MacW.) and is evidenced by the absence of visible systolic expansion of contracted arteries in the body even with a good pulse-pressure.

While maximal oscillation is occurring, some of the systolic rise is being expended in changing the artery from the half-flattened to the circular form by overcoming the extra external pressure which was needed to induce the half-flattened position in the time available between the pulse beats.

All the rest of the systolic rise acts upon the now circular tube, distending it from the zero position to a greater or less extent according to the distending pressure available and the elastic resistance presented by the arterial wall. If the available pressure is equal to the original diastolic pressure the tube will be distended to the diastolic position ; if the available pressure is greater the distension will necessarily go further.

The comparatively small portion of the systolic rise that is spent in changing the half-flattened tube into the circular form is much more effectively used in causing volume change in this way than it would be by adding to the last phase of the expansion of the circular tube from the zero position ; in this last phase the effect of a little more pressure would be very slight as the artery is already considerably distended and the co-efficient of elasticity in its wall increased, at least as far as relaxed or slightly contracted arteries are concerned, while in strongly contracted arteries the whole expansion from the zero position (though relatively greater at higher pressures) is slight as compared with the volume change depending on alteration in the shape of the tube.

When the external pressure is raised to such a height that the artery is completely flattened between the beats the external pressure must equal the diastolic pressure *plus* the resistance which the tube offers against being flattened in the time available between the pulse-beats. In recovering (under the distending force of the pulse pressure) from complete flattening the elastic reaction of the tube fades away as the latter recovers, and as the external pressure remains undiminished some of the pulse-pressure must be used in increasing amount, to bring the tube back to the circular form ; from this point distension has to be carried on against an external pressure which is higher than in the case of half-flattening by the additional external pressure necessary to give the complete flattening. Even in so easily compressible a tube as the relaxed carotid of the sheep the difference in the size of the oscillations with (*a*) half-flattening and (*b*) complete flattening is quite marked, the oscillations being decidedly smaller in the latter, Evidently the excess of external pressure needed to cause complete flattening in the time available between the pulse-beats is sufficient to have a prejudicial effect on the size of the oscillations, interfering seriously with the amount of opening up and expansion of the distensible tube by each systolic rise. (Fig. 14.)

Development of oscillations when the pressure on the exterior of an artery is gradually raised. As the external pressure is increased, reducing the size

of the artery between the beats, the oscillations grow in size till the zero position of the arterial tube is reached between the pulse-beats ; the distension at each beat approaches or reaches or overpasses the diastolic position according as the amount of the pulse pressure approaches or equals or exceeds the original diastolic pressure.

With further elevation of the external pressure partial flattening of the artery between the beats begins, and the oscillations increase, often with some suddenness, being augmented by the volume change involved in flattening and recovery of the circular form. With external pressure increments of 5 mm. Hg. the development of flattening is apt to be sudden, if the increment acts on a vessel already at the zero size. But if the last increment falls short of establishing the zero position say by 2 or 3 mm., then only 2-3 mm. of the next increment are available for causing flattening, and the increase in the size of the oscillations may not be so sharp. Much depends on the resistance offered by the arterial wall in relation to the periods during which the pressures act.

Non-distensible tube or artery. Here the only volume change possible is by flattening to various extents and the recovery from the same. The greatest possible displacement will of course be got with complete flattening, when the pulse pressure is sufficient to open (within the time available) up the tube to its original circular form against the external pressure necessary to cause complete flattening between the beats.

In such tubes we have found by experiment that the maximum oscillation occurs when the external pressure is raised to such an extent as to cause complete or almost complete flattening between the systoles ; this constitutes a notable difference from what obtains in a distensible artery. An external pressure sufficient to cause half-flattening of the non-distensible tube elicits oscillations that are by no means maximal ; the half-flattened position is not the optimum one here. With the complete or almost complete flattening the oscillations are maximal even when the systolic rise does not nearly open up the tube to its circular form between the beats. Further distension of the vessel after the circular form has been restored, which plays a very important part in the volume oscillations of normal arteries, is slight or absent here, according as to whether the loss of distensibility in the artery is more or less complete.

These facts have obviously an important bearing on the study of maximum oscillation in man. Normal arteries, when contracted, and pathological arteries with stiffened or relatively inelastic walls present numerous gradations in character between the highly-distensible and easily compressible tube represented by a normal relaxed artery and a more or less completely non-distensible tube, the latter, while non-distensible by internal pressure, being (*a*) in some instances easily compressible by external pressure, and (*b*) in other instances offering marked resistance to compression by external pressure. It follows, in accordance with the foregoing observations, that there must be, *caeteris paribus,* a similar variation in the behaviour of

these different vessels as regards their pulsatory volume changes under the influence of external pressures.

Further it is to be borne in mind that in pathological conditions arteries are commonly very far from being uniform in character along their length, there being often large variations in shape, calibre, thickness of wall, stiffness, elasticity, &c. Reasoning based on the conception of such vessels as regular cylinders with walls of uniform character is obviously inapplicable in such cases.

Influence of a resistant arterial wall. It is obvious that the amount of resistance to compression offered by the arterial wall must affect the amount of external pressure necessary to cause the requisite amount of flattening in the time available between the systolic waves. Different degrees of resistance, along with defective distensibility, may depend on different degrees of contraction ; as has been described, contraction (or resistance from other causes) can be greatly reduced, if not altogether removed, by repeated or continued compression. The initial raising of the external pressure above the obliteration point, as in the Erlanger method, tends to reduce resistance offered by the arterial wall.

With arteries in the compression tube we have frequently obtained graphic records showing notable differences when taken with a rising external pressure as compared with those obtained during the subsequent lowering of the same pressure ; the differences affect both the position of the maximum phase and the size of the oscillations. With the lowering of the external pressure the maximum phase often comes at a lower level and with enlarged amplitude of excursion. This is probably due to the influence of the preceding compression on the arterial wall.

Martin recorded a result of this kind in the case of an old man with considerable arterial sclerosis, a failing heart and a high systolic pressure (200 mm.), where the maximum oscillation was obtained at the systolic level with the rising external pressure and considerably lower with the falling external pressure. He suggests no explanation of this, but remarks that such variation with the conditions under which the record is taken constitutes a serious indictment against the maximum oscillation method.

The occurrence of maximum oscillation at (or near) the systolic pressure (pulse obliteration), though agreeing with the (discredited) view of Tschlenoff, seems paradoxical. But such is quite conceivable in the case of an artery which is very compressible near its distal end, while resistant and non-distensible (*e.g.*, from strong contraction) along the rest of its length. With such an artery in the compression tube we have sometimes seen the maximum oscillation approaching the systolic (obliteration) level in a remarkable way ; the compressible distal end was closed by an external pressure not much above what was necessary to elicit maximal pulsation in the rest of the tube.

In this connection the position of the arterial wall when maximum oscillation occurs is evidently important. If a restoration of the zero position by external pressure is all that is needed, as is commonly believed at present,

resistance of the wall to compression would not come into play—in contrast to the requirements of a flattened position. In accordance with the view at present held it has been asserted that the maximum oscillation method gives results that are unaffected by the state of the arterial wall. Such a conclusion is obviously unwarrantable.

Influence of the form of the internal pressure curve. If the internal pressure curve is of such a form that the minimal level of pressure is of extremely short duration a higher external pressure will, *caeteris paribus*, be needed in order to establish the half-flattened position between the beats.

Influence of pulsatile changes in length on the oscillation. This factor seems to have been entirely overlooked in the consideration of the question of maximum oscillation. In the application of Marey's principle the behaviour of the tube as regards transverse expansion is what has been discussed.

The volume change depending on pulsatile elongation of an artery varies much in different circumstances ; under certain conditions, with no external pressure applied, &c., the increase from this cause is much larger than that due to transverse expansion, both in contracted and relaxed arteries, the actual volume change being vastly greater in the latter.

If an artery under the influence of the diastolic pressure is bent to one side, either before the systolic rise of pressure or during that phase, the longitudinal expansion is very striking. On the other hand an artery kept straight during the systolic phase by longitudinal tension shows only transverse expansion.

The normal longitudinal tension of an artery between its attachments is tension in an empty tube, the latter being shorter than the distance between its attachments. But the tube when stretched by a certain internal pressure is long enough to cover the distance without longitudinal traction, *i.e.*, with no pull upon its attachments ; of course this involves longitudinal tension of the elements of the arterial wall though applied by internal (blood) pressure instead of external longitudinal traction applied at its ends or attachments.

With a certain amount of longitudinal traction on an artery, between its attachments, the internal diastolic pressure may be just sufficient to counterbalance this, so that there is no longitudinal tension, except that of internal strain, till the systolic rise comes ; the latter would then cause lengthening and bending of the artery. Greater longitudinal traction than could be counterbalanced by the diastolic pressure is necessary to prevent bending in a relaxed artery when the systolic rise comes ; the artery must be already kept stretched between its attachments to an extent as great as would result from the systolic rise of pressure. In other words if an artery is to be kept straight when internal pressure is put on, the tube must be already stretched (by external traction) as much as the internal pressure would lengthen the empty tube.

An artery stretched and bent by internal pressure gradually becomes straightened as the external pressure is raised ; this is strikingly evident when an artery is examined in the compression tube in the usual way, the artery becomes shortened and straightened as the internal pressure becomes counterbalanced by external pressure.

The elongation of an empty artery which occurs with active contraction of its muscular coat is quite a different matter from the transverse and longitudinal expansion simultaneously caused by internal pressure.

When external pressure is applied so as to counterbalance the internal diastolic pressure the artery must pull on its attachments between the pulse-beats, the " passive " tube freed from internal pressure being longitudinally stretched so as to cover the required distance. The systolic rise of pressure must then have relatively little—or at least less—effect in causing elongation. The tube is already stretched by external longitudinal traction, and the rise of internal pressure may not be more, or much more, than would extend the artery to this length.

But if the artery is not stretched between its attachments and the diastolic pressure is counterbalanced by external pressure, the passive tube will elongate much more at the systolic rise. In pathological conditions arteries are often not in a state of tension between their attachments, but are greatly elongated and tortuous under the influence of the internal pressure. Removal of the latter influence by a counterbalancing external pressure causes marked shortening—in arteries that are not changed structurally in such a way as to be incapable of shortening considerably— with much elongation of the passive tube during the systolic rise ; in this case the systolic elongation is not masked by existing longitudinal traction, and volume change due to elongation plays an unusually large part in the genesis of the oscillations.

Martin describes the occurrence of maximum oscillation at sub-diastolic pressures when the artery was insufficiently stretched, the mid-point of a long series of approximately maximal oscillations being taken as the maximal oscillation index ; he offers no explanation of this occurrence. From our own experiments we deduce that maximal oscillation at an unusually low level may be due, in part at least, to the part played by elongation of the loose artery, large volume changes from this cause coming at a relatively early stage ; it does not follow that such low level should be sub-diastolic.

In experiments by one of us (J. A. MacW.[16]) on the elongation of arteries by successive rises of internal pressure or by weights, it was found that contracted arteries gave increasing elongations up to a certain point, and relaxed arteries gave large elongations at several rises from zero, the second being often as large as, or even larger than the first. So it is evident that when external pressure is applied, elongations of large size must occur, in an artery unstretched or insufficiently stretched by traction at its ends, before the diastolic pressure is counterbalanced, *i.e.*, at sub-diastolic external pressures.

We have not in our experiments seen *maximal* oscillations at so low a level as to be actually sub-diastolic, though such might have been assumed if one relied solely on the readings from the minimum manometer on the proximal side of the artery. But in such cases direct inspection showed obvious flattening of the artery, and this made it plain that the external pressure must have exceeded the internal pressure in the artery, the latter being clearly lower than that measured by the proximal manometer ; in such cases the reading of the distal manometer revealed the presence of a considerable gradient in the diastolic pressure, being decidedly below the reading of the proximal manometer. It is to be noted that Martin used an ordinary Hg. manometer to measure the internal pressure and apparently did not measure such pressure on the proximal and distal aspects of the artery.

Volume changes due to elongation must evidently have little or no effect, in the case of forms of apparatus other than the armlet which apply local pressure to a very limited area of the artery (*e.g.*, Oliver's hæmadynamometer, &c.). But these forms have many other causes of variation and fallacy associated with their working.

The decline in the oscillation magnitude from the maximal phase.

A sudden declension in the oscillation magnitude from the maximal or approximately maximal phase is an important feature in many tracings,
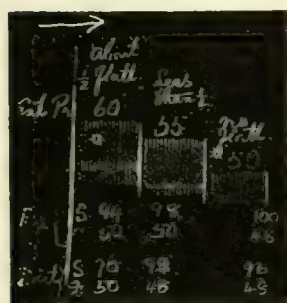
Fig. 15. Carotid, ox. The maximal oscillation occurs with half-flattening, about 10 mm. above the internal diastolic pressure. After the abrupt decline in oscillation magnitude the external pressure is close to the internal diastolic pressure (50 mm.).
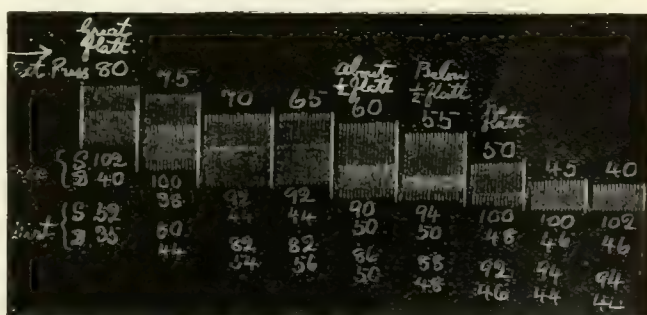
Fig. 16. Carotid, ox (relaxed). Maximum oscillation continues over a range of about 20 mm. (55 to 75 mm. external pressure). After an abrupt decline from maximum oscillation the external pressure (50 mm.) is slightly above the internal diastolic. The appearance of flattening of the artery is noted.

and supplies the Recklinghausen-Erlanger index of diastolic pressure. We find that this declension is related to the cessation of the distortion of the circular tube by the external pressure. (Fig. 15 and 16.) But the absence or dubiousness of this feature constitutes a very serious difficulty in utilising this method, and one that has been widely felt. Such is the case

both with an experimental schema and with the armlet as applied clinically. In regard to the former, see Fig. 17, in which the change is seen to be a gradual one ; and no point can be fixed upon as affording an index of any kind. Such a condition is too familiar in clinical records to need illustration here. Experimentally, we have found such in arteries of very different types (*a*) relatively inelastic (Fig. 18), (*b*) contracted and resistant (Fig. 17), and (*c*) highly distensible relaxed vessels (Fig. 19).

There are various possible causes that may be stated in this connection.

The question of the volume changes due to elongation at each pulse-beat —commonly ignored in this connection—is important. If the conditions are such that elongation contributes largely to the total volume change and at a stage when the external pressure is sub-diastolic, such would tend to obscure the sharpness of the alteration determined by the beginning (or ending) of flattening of the tube.

In the case of a non-distensible tube, where the volume oscillations are due to various degrees of flattening between the beats, there would naturally be no very sharp and striking change at any phase, but rather a progressive alteration in size. (Fig. 18.) The beginning of the flattening would of course be nearer the diastolic pressure than the subsequent phases.

In a tube showing virtually only changes in length at the pulse-beats there would be a graduation in the volume changes at different external pressures—no sudden point of alteration.

With an artery relatively inelastic,* but not absolutely so, the conditions are complex. There are many possibilities, according to the degrees in which the volume changes are contributed to by changes in length, flattening of the tube or change from the diastolic to the zero position, the last named obviously depending on the extent to which the artery is distended by the diastolic pressure before the external pressure is applied.

Again, the character of the arterial wall comes in question—as to whether it is not only relatively inelastic as regards distensibility, but offers, or does not offer, marked resistance to flattening. In the latter instance there might be a sudden and marked alteration in the oscillation values at the point where the slight volume changes dependent on the alterations of the little distended circular tube from the diastolic to the zero position are suddenly augmented by the relatively large displacements associated with flattening of an easily compressible tube.

In a very distensible artery there will be relatively large oscillations, as the external pressure is raised before any flattening occurs ; the amplitude of the oscillation up to that point is indeed a measure of the distensibility of an artery, showing the extent to which it is distended by the diastolic pressure within it.

If the arterial wall offers much resistance to flattening and the increments or decrements of external pressure are small, the latter may be insufficient

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* We mean by this term vessels of defective distensibility that are relatively little affected in transverse diameter by the blood-pressure.

Fig. 17. Carotid, ox, contracted. A series of oscillations is seen, showing approximately maximal size over a considerable range of external pressures (marked below the tracing), with no point of sudden alteration in oscillation magnitude.
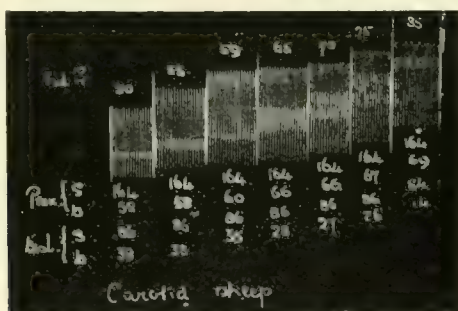
Fig. 18. In this experiment different degrees of flattening were produced in a practically non-distensible artery by rises of external pressure; the first phase (50 mm external pressure) was attended by slight flattening, which increased in amount as the external pressure was raised. The gradual character of the changes in oscillation magnitude is evident. The lowering of the distal diastolic pressures, under the influence of the raised external pressure, is gradual in this case.
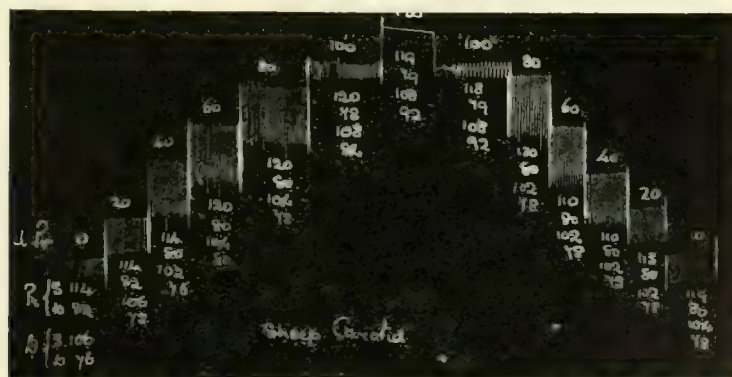
Fig. 19 The change in oscillation magnitude at different external pressures is a gradual one. No fall in the distal pressures is seen. This artery is in the relaxed state.

to cause any sudden and marked alteration in the series of volume changes, at the beginning of the process of flattening, the increment (or decrement) being insufficient to effect the change between the zero and the half-flattened positions, but only to carry it to an intermediate phase, involving a more gradual modification in amplitude.

Again, if the artery, subjected to external pressure, is unequally resistant along its course the necessary degree of flattening may be more or less gradually developed along its length.

Erlanger experimenting with tubes of peritoneal membrane associated the persistence of approximately maximal oscillation over a considerable range of extra-vascular pressure with the indistensible character of such tubes ; and Janeway had noted a similar persistence in cases with sclerosed arteries or high blood-pressure.

In our experiments we have obtained a great extension of the period of practically maximal oscillation not only in non-distensible arteries (not constant in them) but also in highly distensible relaxed arteries. (Fig. 16.)

It is to be borne in mind that in obtaining oscillations from a limb by means of the armlet the conditions are by no means wholly identical with those present when a single artery is tested ; in the limb the various arteries of different sizes and with different pressures and phases of maximum oscillation contribute in varying degrees to the total volume changes recorded by the apparatus.

Relation of maximum oscillation to the mean pressure.

The phase of maximum oscillation has no necessary or constant relation to the mean pressure within the artery.   Under certain conditions there may be a rough correspondence between the mean pressure and the external pressure needed to elicit the maximum oscillation.   But as a rule this is not the case.   Neither the lowest level at which the oscillation is approximately maximal nor the mid-point of that period is a guide to mean pressure, though the latter is much nearer it than the former.

Relation of our results to the view at present accepted.

Our findings in regard to the mechanism of maximum oscillation are subversive of the view at present accepted.*   According to that view the oscillations, largest when sufficient external pressure has been applied to neutralise the internal diastolic pressure and bring the vessel into the zero

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* Many years ago Roy and Adami thought that a pulse wave of 30 mm. Hg. would produce the greatest change in the cubic contents of a portion of artery if at each pulse-beat the artery is alternately collapsed and opened out.   They regarded the external pressure necessary to cause collapse of a radial artery, after excision, as being so small as to be safely negligible in the present connection.

Erlanger from direct observation of a rubber tube subjected to external pressure concluded that the maximum oscillation occurred when the relations of external and internal pressure were such that with each pulse wave the tube opened out to almost its full extent and at the end of diastole the walls just met.

position, decline with raising or lowering of the external pressure from the optimum level. In the former case the external pressure becoming higher than the diastolic pressure tends, as Howell puts it, to overcome the stiffness of the arterial wall ; the pulse wave then has an excess of pressure on the outside to overcome, and this is believed to involve a diminution in the oscillation volume, the movement of the arterial wall being less extensive in proportion to the excess of pressure on the outside, &c. On the other hand, with a falling external pressure only partially neutralising the diastolic pressure the lessening of the volume of the circular tube by the external pressure between the beats is insufficient to allow of the maximum range of systolic expansion ; hence lessened excursions. But there is nothing here to explain the sudden decline from the maximum which often occurs and serves as the Recklinghausen-Erlanger index ; in accordance with the known elastic properties of the arterial wall the decline ought to be a gradual one, depending on gradual alterations in the amount of expansion of the circular tube, such as are found experimentally when an artery is tested with definite increments or decrements of internal pressure.

According to our view the maximal oscillation only occurs when the artery is flattened between the pulse beats to a very considerable extent, e.g., to half-flattening in an easily distensible tube, to complete or nearly complete flattening in a non-distensible one.

A higher external pressure causes diminished oscillation, by producing excessive flattening in a distensible artery and opposing too much resistance to systolic expansion. A lowered external pressure fails to cause any distortion of the circular tube between the beats ; the systolic expansion is represented by increased distension of that tube and is sub-maximal. Often the change between the latter form of expansion and that compounded of such expansion and the opening up of a partially flattened tube is sharply marked and in our view constitutes the real basis of the Recklinghausen-Erlanger index.

But according to this interpretation the index ought not to be the usual one of taking the lowest level at which oscillation is maximal, but the level at which the markedly diminished excursions are first obtained ; at this level the external pressure balances, more or less exactly, the internal diastolic, but does not exceed it sufficiently to cause distortion of the circular tube. In many of our experiments we have found this index to approach more closely to the actual diastolic pressures in the artery.

PART II.

THE AUSCULTATORY OR AUDITORY METHOD.

The auscultatory method of estimating blood-pressure proposed by Korotkoff[13] of St. Petersburg in 1905 has received comparatively little attention in this country—much less than in Germany.

Oliver[21] has described the method and devised a convenient tambour for use instead of a stethoscope.

As far as systolic estimation is concerned, all observers who have worked with this method seem to be pretty well agreed that it yields accurate indications ; most observers find it more precise than the ordinary tactile method, though Gibson thinks that it cannot replace the latter.

In regard to diastolic pressure there is much uncertainty as to the indications yielded by this method. There are conflicting views as to which phase is to be regarded as the diastolic index. Thus Ettinger[6] regards the disappearance of all sounds when the armlet pressure is gradually lowered as corresponding to the minimal or diastolic pressure, while Fischer[7] believes that the latter is indicated by a change in the character of the sound (from clear to dull) some distance above the point of disappearance.

Oliver, while disposed to regard the lower limit of the sound as the diastolic index, says that there is not the same assurance on this point as in regard to the systolic index.

Lauder Brunton[2] says that the diastolic pressure may correspond to the level of a rising external pressure at which the sound appears loudly—the point where the sound increases being generally sharply marked—to disappear or at least become much feebler at a higher level ; or on the other hand, that the true diastolic pressure may correspond with the loudest intensity of the sound. He remarks that experiments on animals or on a schema are needed to determine what relation the sudden increase of the sound on raising the external pressure bears to the diastolic pressure.

There is not, as far as we are aware, an investigation, under precise experimental conditions, of the auscultatory manifestations in relation with :

(*a*) accurately measured internal pressures (systolic and diastolic), taken on both the proximal and the distal side of the artery ;

(*b*) direct observation of the behaviour of the arterial walls ; and

(*c*) the varying degrees of oscillation in arterial volume (maximal pulsation, &c.).

Character of the sounds.

Between the upper and the lower limits of the sound production very marked variations in character and intensity are recognisable, and these show considerable differences in various circulatory conditions.

Ettinger described five phases during the lowering of the external pressure from above the obliteration point.

(1) The beginning of the sound in the form of a clear-cut sound occurring in the systolic phase, and serving as an index of systolic pressure, beginning with the passage of the first waves of blood through the artery under the armlet.

(2) A murmur of variable duration replacing the first sound.

(3) A clear sound, replacing the murmur.

(4) A transformation of the clear sound into a dull one, this change sometimes being sharply defined, at other times more gradual.

(5) Disappearance of sound.

Kryloff had previously given an account of the first three phases only. Gittings'[9] experience agreed with that of Ettinger.

Oliver describes four successive phases between the appearance and disappearance of the sound or throb, characterised by (1) sharpness, (2) murmurishness, (3) loudness, and (4) dullness. We find that an essentially similar series of sounds can be studied on an experimental schema.

Views as to the production of the sounds.

Great importance has been attached in this connection to what occurs in the artery below the seat of compression by Korotkoff and other observers. According to Korotkoff the lower portion of the brachial artery is relaxed* while the artery higher up is obliterated by the armlet, and when the first blood waves come through (on lowering the armlet pressure) the sudden stretching of the artery lower down causes the production of sounds.

Kryloff† describes the first sound as the loudest, and puts this down to the smallness of the lumen in the artery under the armlet at this phase, and the consequent rapidity of the blood-current through it ; this he looks upon as favouring a sudden stretching of the walls of the vessel below the armlet.

Ettinger considers the vibration to be more pronounced in the third phase and ascribes this to the larger volume of blood passing under the armlet, though with diminished rapidity, at this period.

Ehret regards the suddenness of the distension, and not the amplitude of the pulse-wave, as essentially affecting the intensity of the sounds. The speedy diminution of the sounds below the armlet is attributed to the less complete emptying of the artery.

To the suggestion that the sounds are really transmitted heart sounds, Kryloff opposed the consideration that all sounds disappear when the armlet pressure is lowered beyond a certain point.

Gittings favours the view that the sudden stretching of the relaxed vessel wall is the cause of the first sound. He also attaches much importance to the size and accessibility of the artery, being able to hear the sound only in exceptional instances and only for a short time over the radial or ulnar artery when the armlet was applied to the forearm. He also regards the resonating character of the armlet as a very important factor, finding that with simple compression by an Esmarch bandage the sounds are not as a rule audible.

Oliver thinks that sound is developed when the external pressure falls below the obliteration point from jets of blood being projected through a narrowed lumen into comparatively empty vessels, their impact against the relaxed walls being audible as a throb. He ascribes the variations in the quality of the throb to different amounts of blood in the relatively collapsed arteries, the varying calibre of the lumen compressed, and variations in the rapidity of the current.

Experiments with a circulatory schema.

In order to study the auscultatory phenomena and their relationships with internal pressures, oscillation of the arterial walls, &c., we have employed an arrangement similar to that described with regard to the maximum oscillation method. The rotating tap already mentioned was always used in these experiments to give the pulsatile flow ; in this way the danger of confusion from sounds produced by a pump or the valves of a syringe, &c., was avoided.

Distally to the compression tube and quite close to it a piece of relaxed carotid (sheep) was often interposed and the auditory tambour or phonendo-scope applied over it. In other cases the sounds were listened for over the glass tube emerging through the rubber cork at the distal end of the compression tube. The sheep's carotid was most commonly used in the compression tube ; the horse's metacarpal and the carotids of the ox and horse being also tried. The former two were found to be the most suitable, especially the first.

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* The term " relaxed " here presumably means an undistended condition of the artery, not an inactive condition of the arterial-muscle—the strict meaning of the word " relaxed."

† Quoted in Gittings' paper (Arch. of internal Medicine, 1912, vi, 196). We have not been able to see Kryloff's original communication.

With an artery (*e.g.*, carotid of sheep) in the compression tube under accurately known conditions of internal and external pressure we have correlated (*a*) the visible changes (alterations in form, vibration, &c.), in the vessel with (*b*) the sound production in different circumstances, while making simultaneous observations of (*c*) the pulsatory volume oscillation (by graphic records) and (*d*) of the occurrence of thrill, &c.

On gradually raising the external pressure, so as to cause progressive diminutions in the size of the artery from the original distension by the diastolic pressure to the zero position, no sounds are audible ; during this period the volume oscillations are gradually augmenting, but are still markedly short of the maximal size. It is only when the external pressure is further raised so as to cause some visible flattening of the circular tube in the diastolic intervals that a sound occurs with each pulse-beat (lower limit). At this point the volume oscillations are still far from maximal. Progressive augmentation of the external pressure leads to more extensive flattening and increased loudness of the sound, then the development of a murmur, the substitution of a single sound for the murmur, and finally the disappearance of this sound (upper limit). The phases of the maximum intensity of the sound or murmur are associated with extensive flattening, with very obvious vibrations of the arterial walls (often with a sensation of thrill on palpation) and large, it may be maximal, volume oscillations. The extinction of the sound is seen to coincide with a condition of complete flattening and obliteration, present even during systole, and attended by a great diminution of the volume oscillations.

On lowering the pressure from above the obliteration point the same series of changes in reversed order presents itself. The sound begins as soon as a certain amount is forced through the compressed area at each systole, this being attended by a more or less marked increase of volume oscillation— the Erlanger systolic index. The lower limit of the sound is found to coincide with the phase where the external pressure has been lowered to such a point that it just fails to cause any obvious effect in distorting the circular form of the tube in the diastolic intervals. The plan of following the changes from above downwards is to be preferred in the application of the auditory method, for in this way it is commonly possible to follow the sounds downwards to a lower level of the falling external pressure, than when one listens for the beginning of the sound with a rising external pressure.

It is quite clear that the sound production at its lower limit occurs when the external pressure exceeds the internal diastolic pressure by the amount, generally very small, required to cause slight flattening, an amount decidedly less than is needed to produce the more extensive distortion associated with maximum oscillation, with the associated murmur, thrill, &c. (Fig. 20.)

For example, with proximal pressures of 100 mm. systolic and 64 diastolic and distal pressures of 80 mm. systolic and 60 diastolic, the sound was heard distinctly while the external pressure was at 64 mm., but was not audible when the external pressure had been lowered to 62.
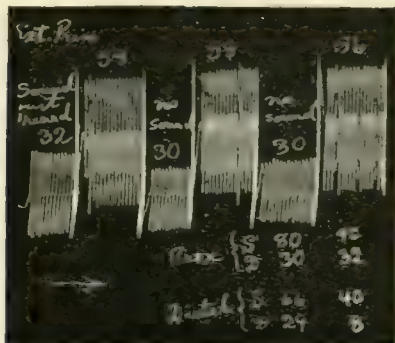
Fig. 20. The maximum oscillation, attended by a loud murmur, occurred with an external pressure much (16–18 mm.) above the internal diastolic pressure as measured manometrically and indicated accurately by the disappearance of the sound. External pressures marked above the tracing.

The evidence available from various sources renders it certain that the mid-point of the period of approximately maximal oscillation does not afford any correct indication of the internal diastolic pressure. It is as a rule decidedly too high ; in very many cases the over-estimate is an extensive one. The auscultatory index (lower limit of the sound) is always lower and corresponds more nearly with the sudden decline in oscillation magnitude, when such occurs in a sufficiently marked and characteristic form to yield reliable indications.

The auditory diastolic index comes decidedly below the level of external pressure at which marked disturbance of the distal pressure—in relation to the proximal pressure—occurs as already described when dealing with the maximal oscillation. The absence of this complication renders it possible in a schema to correlate the relations of sound and the intravascular pressures more accurately.

Production of the sounds.

As has already been stated great importance, in regard to the production of the sound, has been attached by observers to the behaviour of the brachial artery below the compressed area—the sudden distension of a more or less lax artery. But we find that on gradually raising the external pressure the sound begins when the artery is only slightly flattened, so that there is no appreciable interference with the flow through it and no change in the systolic or diastolic pressures in the artery beyond. Hence there is at this time nothing to cause imperfect filling of a lax artery beyond, with the possibility of sudden distension at the systolic—beyond the ordinary systolic distension which takes place in any artery with no external pressure applied, and in which no sound is produced. The same holds good in regard to the sound production near its lower limit, when the external pressure is gradually lowered.

When using an artery in the compression tube in the way described, with no piece of artery on the distal side, but the phonendoscope or tambour applied over the glass tube issuing from the artery in the compression tube, we find that the sounds are perfectly well developed and characteristic— a fact which controverts the idea of the essential importance of the artery distally to the compressed area.

Experiments with rubber tubes of the ordinary kinds we used were found to be unsatisfactory ; with special thin-walled tubing the result might be different.   Under the influence of different heights of external pressure in the compression tube or armlet, the tube showed flattening to various extents between the systoles with blowing sounds, &c., but not the characteristic sound production ; the volume changes much resembled those in an extremely resistant and non-distensile artery, and the changes in the internal pressures (distal especially) were similar.   Under such conditions a length (20 cm., &c.) of sheep's carotid (relaxed) which readily gave the characteristic sounds when tested in the compression tube, was placed distally to the compression tube and close to it.   The pressure and flow in this distal artery (*i.e.*, the artery below the seat of compression) was markedly affected by the action of certain heights of external pressure on the rubber tube (obliteration, half-flattening, &c., in the latter), but no sound was audible at any part of it.   Sudden variations in the distension of this artery due to changes in the degree of compression of the rubber tube were not accompanied by the characteristic sounds.

It is indeed not easy to conceive how such sound could be produced from the further distension of an elastic artery of circular form any more than by the normal systolic expansion of a very distensile artery (relaxed, &c.) with no external pressure applied.

Evidence as to the sound production is also obtainable from examination (in man) of the effects of compression of a very limited area of the artery, instead of the extended compression by the armlet.   We find that the sound is quite audible though relatively feeble when suitable pressure is applied to the brachial with the finger.   The feebleness of the sound in this case is opposed to the current view of the sound production.   For if the condition of the artery on the distal side ("empty" or lax, undistended, &c.), is the essential point, the sound ought to be well developed, the condition of the distal artery being capable of being affected in the same way by compression higher up, whether it is by the armlet or the finger—the blood-stream reaching the distal artery is similarly affected in both cases.   The great influence of the length of artery subjected to compression points to the importance of that area as the seat of sound production.

With reference to the possible influence of the air in the armlet as a resonating medium, to which much importance has been attached by Gittings, we find that the sounds are quite well marked when the artery in the compression tube is not in relation with an air cushion at all, the whole space around the artery and the tubes connected with the compression tube

being entirely filled with liquid. The loud murmur attended by very obvious vibration of the arterial walls, occurs with a suitable external pressure under these circumstances in characteristic fashion.

As regards the timing of the sounds we find that the position of the latter in the cycle of changes at each pulse-beat may under certain circumstances vary considerably, sometimes coming early in the systolic phase, sometimes much later—towards the end of this phase, &c.

In addition to a study of the phenomena observable during the succession of systolic and diastolic phases recurring at the rates of pulsation (60, 80, &c., per min.) we have tried the effects of maintaining these phases for longer periods, the stream being more or less suddenly turned on and kept flowing for some time, then turned off with varying degrees of suddenness ; in this way it can be tested whether the sounds are due to a sudden rise or a sudden fall of internal pressure setting up vibration in the arterial walls, &c. ; various levels of external pressure are maintained during these observations.

It was found that, with a suitable external pressure, the sound is generally produced when the pressure is turned on, *i.e.*, at the systolic phase, though with certain arrangements in the experimental schema we noted the production of sound in the diastolic phase.

Under certain conditions sound is not only audible when the pressure is turned on, but persists as a continuous murmur as long as the stream is kept flowing through the artery, while a certain level of external pressure is kept up ; lowering of the external pressure causes the murmur to be replaced by a single sound when the internal pressure is turned on. With too low or too high an external pressure no sound is heard. The murmur varies markedly in pitch, being of higher pitch with a higher external pressure. Accompanying the murmur there is a remarkable amount of thrill which can be felt with the hand applied to the compression tube or to one of the tubes leading to or from the artery. Active vibration of the arterial walls is very obvious on direct inspection, and is plainly evident in the column of fluid in a vertical glass tube connected with the stream distally to the compression tube. The rate of oscillation of the fluid in the vertical tube alters strikingly with the variations in the pitch of the murmur ; this is determined by changes in the height of the external pressure within certain limits.

These facts recall the vibratory or purring sensation that can often be recognised with the hand applied over some of the larger arteries in cases of aortic regurgitation.

Indication of arterial distensibility.

As the declension of the sound serves as a guide to the beginning of appreciable flattening it is evident that an indication of the distensibility of an artery is afforded by the extent of the oscillation elicited in presence of a fair systolic wave—by raising the external pressure to the level at which

the auditory diastolic index is obtained. The possible oscillation range up to that point varies with the extent to which the arterial volume has been enlarged by the internal diastolic pressure before the external pressure was applied. Of course the amount of the distending force at each beat as indicated by the pulse-pressure is an essential factor in this connection ; a pulse-pressure of higher value than that of the original diastolic pressure will cause, under clinical conditions, expansion beyond the diastolic position. The amount of this will vary according as the artery yields much or little to the further increase of pressure ; this will be influenced by the height of the diastolic pressure and the amount of distension produced by it, for an artery already much distended by a high diastolic pressure will yield proportionately little to a further (systolic) rise of pressure.

We have made observations of this kind both under clinical conditions and with excised arteries.

A modification of the compression tube method.

The advantages of the compression tube method are obviously great, the behaviour of the artery under different external pressures being open to direct inspection, while the volume changes are recorded graphically, the sounds heard, the internal pressures measured, &c. But there is one point of notable difference from the conditions present when an armlet is applied to a human limb in the usual way, inasmuch as in the compression tube the ends of the artery are tied on rigid (glass) tubes, which keep them open even when the rest of the vessel is more or less completely closed by a high external pressure. Of course in a limb the artery outside the area of compression, proximal and distal to the armlet, remains open, but there is not the same rigidity at the junction of the compressed and the non-compressed (circular) portions of the tube. As it is plain from direct inspection of the artery in the compression tube that at certain phases the movements of the arterial walls are specially extensive and vigorous near the ends it is very possible that an important influence on sound production may be exercised by those portions of the vessel under the special conditions in which they are placed.

A method of eliminating this possibly disturbing influence of the glass tubes is to use an artery which has been prepared in a special way. Its distal and proximal ends where tied on the glass tubes are treated, for a distance of about a centimetre, with formalin, and thus rendered much more resistant than the rest of the vessel, with the result that when the external pressure is gradually raised the main part of the artery becomes flattened, while the terminal portions still remain circular, the latter corresponding in this respect to the artery below (or above) the armlet in ordinary blood-pressure estimations in man. The movements (flattening and recovery) of the artery in the compression tube are in this way removed some distance from the ends of the glass tubes and uncomplicated by the possible influence

of the physical conditions associated with the direct attachment of the moving arterial walls to the rigid tube.

When tested in this way the auditory method yielded very definite results. The sounds, though weaker and differing somewhat in character from those heard by the first described method, presented the essential features of well-defined upper and lower limits with an intervening murmur phase, &c. The upper limit served well as a systolic index, and the lower quite as well as a diastolic index, yielding definite indications of the actual internal pressures as measured manometrically.

When an arrangement of this sort was used a modification was sometimes made by adding a length of artery (12-14 cm., &c.) on the distal side of the compression tube, to represent the continuation of the human artery distally to the armlet. The added length of artery had previously been tested in the compression tube in the usual way and found to give the characteristic sounds in very marked fashion. This distally-placed artery underwent marked changes when the artery in the compression tube was subjected to sufficient external pressure. But either no sound, or no intensification of the sound already found to be produced in the compression tube, could be heard, when one listened over the early part of the distally-placed artery.

There was not the slightest indication of sound production distally to the compression tube, though the artery placed there was undergoing changes in internal pressure very similar to those present in a human artery distally to the armlet. Sounds heard at the beginning of this artery were much less pronounced than those heard over the short glass tube connecting the artery placed within the compression tube with the distally-placed length of artery ; sound heard at the beginning of the latter was evidently transmitted from the artery in the compression tube and rapidly faded away on listening a little further along the vessel in the distal direction.

The indisputable fact that closure of the artery on the distal side of the armlet and some little distance away abolishes the sounds has been construed in favour of the current view of sound production. Ehret, for example, contends that in this condition the changes in the artery actually compressed by the armlet are much the same as usual, while those in the distal portion of the artery distally are much modified ; he regards this as proving that the seat of the normal sound production is in the distal portion.

Our own observations upon arteries (examined in the compression tube in the way described) have shown that when the artery is closed on the distal side the changes in the part subjected to external compression are influenced notably and in a fashion similar to the distal portion, though perhaps not so extensively.

Further, we attach great importance to the presence of an active flow through the vessel in the normal process of sound production ; the absence of flow depending on distal closure of the artery would naturally be accompanied by an upset of the conditions in which the ordinary sound is present.

The current reasoning as to the production of the sounds in the early part of the artery lying distally to the compressed area postulates the occurrence of extensive changes in this part, depending on the influence of compression of the vessel by the armlet higher up. The distal artery is assumed to be more or less collapsed, and then the sudden distension by the pulse-wave is the reputed cause of the sound. In regard to this it is necessary to bear in mind that the conditions are very different near the lower limit of sound production as compared with the higher phases (*i.e.*, at higher external pressures in the armlet). When the compressing pressure is gradually lowered from the obliteration level, the first systolic jets of blood forcing through the compressed area enter a relatively undistended distal artery, the pressure in which is low, being the residual pressure in the vessels of the part of the limb peripheral to the occluding armlet. The exact amount of such residual pressure will vary according as the armlet has been slowly or quickly inflated to the obliteration point ; in the former case the venous return will be obstructed for a considerable time before the arterial inflow is arrested, and so the vessels in that area become congested. With rapid inflation the residual pressure is less. But in any case there is such pressure present in the distal portion of the brachial artery as to keep the tube in the circular form, unless in presence of some distorting force such as traction upon its ends or attachments sufficient to cause flattening in spite of the influence of the internal pressure. It is difficult to believe that the sound is produced by the sudden distension of an uncompressed artery which is in the circular form ; such does not occur in a relaxed artery undergoing change of this sort under the influence of the pulse-pressure, apart from the presence of external pressure. If such is the genesis of the sound in question why should an ordinary relaxed artery in a limb or elsewhere not give similar sounds when suddenly distended by a good systolic rise ? Resonance by the air in the armlet can hardly affect sound produced in the distal artery, whatever it might do in regard to sounds arising in the length of artery compressed by the armlet. (See also p. 190.)

Again, if sudden distension of the distal artery can be a source of sound, is there any good ground for excluding the artery compressed by the armlet from sound production, especially when rapid changes from the flattened to the circular form and *vice versa* come into play—the changes that are essentially associated with sound production in an artery enclosed in the compression tube as already described.

Current views as to sound production in the distal artery based on the assumption that this part is lax and undistended obviously fail to afford any feasible explanation of sound production at and near its lower limit. For at that phase it is quite clear from our experimental evidence that the pressures (systolic and diastolic) in the distal artery are not influenced by the compressing pressure higher up ; there is no obstruction or interference with the flow through the compressed area, and the distal artery is quite in its normal condition as regards distension, &c., instead of being lax or undistended

or relatively empty and specially susceptible of sudden distension by the systolic wave, as is involved in the current hypothesis.

Experiments on excised arteries by the armlet method.

We have performed such experiments in addition to those with the compression tube as already described. With a rising external pressure the flattening of the artery begins near the distal end and the movements are most active there while the external pressure is raised to a considerable distance ; near the systolic (obliteration) level, on the other hand, the movements are most pronounced near the proximal end, or confined to that end. In the intermediate period there is active movement (flattening and recovery) along the whole length of the vessel, at least in the case of an artery presenting no great differences in resistance along its length.

We have embedded a length of artery (*e.g.*, 20 cm.) in a portion of an animal's limb (ox, &c.) so as to lie in relation to the bone much as the brachial artery is in relation to the humerus in man. The armlet was then applied in the usual way. The artery was introduced into the circuit of the schema, the compression tube being omitted ; the arrangement of the proximal and distal manometers was the same as before. Auscultation was used near the emergence of the artery from the area compressed by the armlet.

The sounds heard with this arrangement were much less loud than with the preceding method of experiment, and somewhat different in character, but the upper and lower limits of the sound were found to correspond very closely with the systolic and diastolic levels as already described.

Definition of the diastolic index in man.

During gradual lowering of the armlet pressure from the region (intermediate between systolic and diastolic pressures) where the sound is very loud, there comes at a certain level a sudden and marked alteration in the sound, which becomes diminished in intensity and duller in character. This alteration may be succeeded (1) by a continued persistence of the altered sound through an extensive further lowering (*e.g.*, 20-30 mm.) of the armlet pressure, or (2) by a speedy or almost immediate extinction of the sound. The alteration in question is, as we have evidence to show, the index of diastolic pressure. In other words the diastolic index is a sudden declension in the sound, which may or may not be speedily followed by its extinction. Such declension occurs when the armlet pressure is no longer sufficient to cause distortion of the arterial tube from the circular form.

In very many healthy persons, in a majority of the young adults (students) examined in a *quiet* room, the sound was found to persist as in

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In a young adult in fair health, with no sign of aortic regurgitation, a persistent sound was audible over the brachial when there was no armlet pressure at all The diastolic index above-mentioned was distinctly got at about 60 mm.

(1) to excessively low levels, retaining the character of a dull thud, quite distinct though weak, down to such levels of armlet pressure as 28, 32 mm., &c. Here the lower limit of the sound is obviously no indication of diastolic pressure, but is very far below the latter. The diastolic index is afforded by the marked change from a sharp to a duller and less loud sound occurring at a much higher level (*e.g.*, 60 mm., &c.).

From the results obtained in such cases it is clear that there may be conditions in the human subject under which sound production may persist after the armlet pressure has fallen below the amount necessary to cause any flattening of the circular tube, but still suffices to diminish to some extent the calibre of the artery from the diastolic size, the arterial wall being brought into a position intermediate between the diastolic and zero positions. Here the segment of vessel included under the armlet, though still circular, is diminished in size as compared with the artery on the proximal and distal sides of the area compressed by the armlet.

In the great majority of cases examined in hospital wards where absolute quiet was not attainable, and also in many healthy and diseased persons examined in a quiet room, the results were such as are indicated under (2), closely resembling those obtained with the experimental schema. (In the latter absolute quiet was not usually attainable.)

We have correlated the data obtained by the auditory method with those supplied by an extended series of observations by the oscillation method on normal and pathological subjects carried out by workers in this laboratory. The results of these observations will be published later.

Limitations and sources of fallacy in the auditory method.

These are in our experience relatively few and unimportant.

1. We have found experimentally that very large and extremely distensible tubes like the relaxed and softened carotid of the ox and horse and stiff thick-walled strongly contracted carotids of the same animals do not give satisfactory results by this method. But the conditions in such experiments are very extreme and far removed from what may possibly be found in man, and we have not found any evidence of similar failure to obtain definite results in thickened and stiffened arteries under clinical conditions.

2. The auditory method is not applicable in many cases of aortic regurgitation on account of the continued presence—apart from the application of external pressure by the armlet—of the well-known sound.

3. We have seen abundant evidence (experimental and clinical) that a very defective rush of fluid through the artery under examination can impair the validity of the auscultatory criteria. Such may result from various causes such as the following :—(a) Congestion and stagnation of blood in the limb distally to the armlet as a result of keeping on the constriction

too long. This also causes the artery distal to the armlet to be much more filled up with blood (*i.e.*, at higher internal pressure) than in the ordinary procedure. (*b*) Excessively small calibre from thickening, constriction, &c., of the artery examined or of its continuation. (*c*) An extremely low pulse-pressure, due to very small cardiac output (feeble heart, very excessive pulse-rate, &c.) with relaxed peripheral vessels, &c.

4. While the brachial artery is excellently adapted for this method, application of the armlet to the forearm gives unsatisfactory results. The range of sound heard over the radial artery is defective, being shortened both above and below, *i.e.*, the systolic index is too low and the diastolic too high. That the systolic reading is too low is shown by comparison with the tactile or the visual index. This would naturally be associated with a similar defect at the lower limit, the sound being cut down too soon. That such is the case is corroborated by the fact that the diastolic reading thus obtained is higher in the forearm than in the arm—an obvious error in the former.

5. The possibility of conduction of the sound along a bone occasionally comes into question both as regards the systolic and the diastolic index. On this point one of us (G.S.M.) and Mr. J. R. Murray have obtained evidence which will be stated elsewhere.

It need only be stated here that with the routine procedure recommended below there is no danger of error in this way.

6. Improper adjustment of the auditory tambour, &c., might possibly lead to inaccuracy, but not when the tambour is properly situated with no appreciable pressure.

In all the conditions mentioned the sound declines too soon when the external pressure is being lowered, thus making the reading of diastolic pressure too high. But the same causes lead to the appearance of the systolic sound—when the pressure is lowered from that causing complete obliteration —being delayed, and so underestimating the actual systolic pressure.

Such an undue lowering of the upper limit of the sound is readily recognisable by using the tactile systolic index simultaneously, and this affords a most important indication of the unreliability of the sudden declension as an index of diastolic pressure.

We adopt and recommend as a routine procedure the simultaneous determination of (1) the reappearance of the pulse by the ordinary tactile method, and (2) the auditory systolic index, as a method of verifying the correct arrangement of the auditory apparatus (tambour, &c.) and its applicability to the conditions present in any particular case.

In doubtful cases, when dealing with arteries that are abnormally thick or contracted, offering considerable resistance on palpation when the internal blood-pressure is excluded, the method of local compression as recommended in a former paper, is very useful in checking the systolic readings, being equally applicable to the tactile and the auditory estimations. (*Heart*, IV, 279.)

We have not in our experimental schema found the sound persisting at so low a level as to underestimate the actual diastolic pressure in the vessel. When there is a considerable pressure gradient in the stream, the diastolic index may sometimes be got below the reading of the proximal minimum manometer, but never below the average between the proximal and distal manometers, and obviously not below the actual diastolic pressure in the artery ; the distinct flattening occurring in the latter shows that the extra-vascular pressure is somewhat in excess of the intra-vascular diastolic pressure—by the amount necessary to cause the distortion in the tube.

But as has already been stated conditions may be present in the human limb which lead to a persistence of the sound (as tested in quiet surroundings) far below the level of diastolic pressure, the latter being indicated by a sudden weakening or dulling of the sound, not its extinction. In other conditions the extinction nearly coincides with the sudden alteration just referred to.

We have very often used Oliver's tambour for attaching over the artery on the distal aspect of the armlet ; this has the advantage of leaving the hands of the observer free. Instead of this we have often used a phonendoscope or a binaural stethoscope. For conveniently graduating the application of the external pressure Oliver's screw-compressor when employed with a suitable armlet (with a rubber bag of not too large capacity) is very useful.

Advantages of the auscultatory method.

Comparing the auditory method of diastolic pressure estimation with the maximum oscillation method as represented by the best graphically recording apparatus in use (Erlanger's), the superiority of the former is conspicuous in many respects.

(1) The simplicity and quickness of the procedure are obviously very great considerations, dispensing as it does with the relatively cumbrous apparatus of smoked drum, recording tambour, &c.

(2) The greater definiteness of the index, as compared with the frequent difficulty and uncertainty of the Recklinghausen-Erlanger index.

(3) The greater constancy of the results. Apart from movements of the limb, the Erlanger record is apt to vary much, and this is not surprising in view of the complexity of the conditions which may be present and play a part in influencing the oscillations, as has already been described.

The auditory index is much less disturbed by alterations in the arterial walls (resistance, distensibility, &c.) ; this naturally results from the required degree of flattening of the arterial tube being very much less than in the other method, while in a vessel presenting unequal resistance along its course, change from the circular form in a comparatively short piece suffices to produce

a sound, while flattening along the whole or the greater part is needed to give maximal oscillations ; numerous influences may tend to give a gradation in the development of the oscillation, and an absence of any sudden and striking change in the size of the oscillations.   The greater degree of flattening approaching complete flattening necessary to give maximal oscillation in a practically non-distensible tube is an important factor, while the form of the pulse curve may also be such as to aid in increasing the excess of external pressure required.   The varying influence of volume changes due to elongation does not come into question in the auditory method.

(4) The avoidance of the discomfort and disturbance (circulatory, &c.) which may be caused by the constriction of the limb when the pressure is raised well above the obliteration point to begin with and during the lowering of the pressure while the graphic record is being made.

Systolic and diastolic pressure estimations.

The estimation of diastolic pressure by the auscultatory method is a process that takes very little time and trouble and yields very definite and valuable information.   The procedure is one calculated to produce less circulatory disturbance in abnormally sensitive cases than the stronger (obliterative) constriction of a comparatively large vascular area involved in systolic determination.

Moreover diastolic estimation is much less, if to any appreciable extent at all, affected by the main sources of fallacy in systolic estimation— variations in the resistance of the arterial wall, possibility of reflected waves, &c.

Even comparatively slight changes in diastolic pressure, unless dependent on alterations in the pulse-rate, are of considerable significance as indications of circulatory conditions (changes in peripheral resistance, &c.).

We have to thank Dr. J. E. Kesson for valuable assistance in the earlier experiments of this investigation.

CONCLUSIONS.

The current view, founded on Marey's principle, that maximum oscillation (or pulsation) occurs when the external pressure counterbalances the internal diastolic pressure so as to bring the artery to the size of the undistended tube is erroneous.

With a normal distensible and elastic artery maximum oscillation occurs when the external pressure is sufficient to distort the arterial tube so as to produce the condition which we have termed half-flattening—in which the shorter diameter is roughly about half that of the undistended tube. The volume of the oscillation is compounded of (*a*) the difference in capacity between the half-flattened and the circular tube, (*b*) the distension of the latter caused by the systolic wave and (*c*) such volume change as may result

from longitudinal expansion at each pulse-beat. Variations in (c) are not adequately represented in experiments that have been made on the arteries of animals *in situ*.

With a more or less non-distensible tube volume oscillations are more or less completely due to different degrees of flattening, a higher external pressure being needed to bring out the maximum effect.

Maximum oscillation does not serve as a guide to the mean pressure within the artery ; there is no necessary or constant relation between the two.

The development and position of the maximum oscillation varies much, being readily influenced by a variety of conditions affecting one or more of the components of the volume changes, *e.g.*, such conditions as (*a*) the distensibility and flexibility of the arterial walls, (*b*) the time available between the beats, (*c*) the form of the internal pressure curve, and (*d*) the part played by elongation of the vessel at each beat.

Maximum oscillation occurs at levels of external pressure above, and often very considerably above, the actual internal diastolic pressure, the excess varying between a few mm. Hg. and 20 mm. or more.

The taking of the mid-point in the period of approximately maximal oscillation is an erroneous method of gauging internal diastolic pressure, widely varying overestimates being thus obtained.

The differentiation (during the lowering of the external pressure) of the last phase at which the oscillation is maximal (the Recklinghausen-Erlanger index) is often uncertain or impracticable. When a characteristic change in oscillation magnitude is clearly recognisable it affords a valuable index. We regard the level of external pressure just *after* the abrupt diminution has taken place as the better guide. This external pressure is just insufficient to cause any flattening.

Methods of estimating diastolic pressure by examination (palpatory or graphic) of changes occurring in the artery peripheral to the armlet (Strassburger, Masing, Sahli, Bingel) are not to be recommended, the indications being dubious and their interpretation unreliable. The same is to be said of subjective change in the sense of throb in the limb as an indication.

The sounds concerned in the auscultatory or auditory method of blood-pressure estimation (diastolic and systolic) owe their origin to vibration of the arterial wall when the normal circular form of the vessel is, in the compression area, more or less distorted by external pressure. The level of armlet pressure at which the sound suddenly declines, becoming weaker and duller, is to be taken as the index of intra-arterial diastolic pressure ; at this level the external pressure has become insufficient to cause any flattening of the circular tube.

The auditory method provides a quick and simple method of approximately estimating the diastolic pressure, more precise and easily interpreted and less disturbed by abnormal conditions than the indications (visual, graphic, &c.), yielded by other methods, rendering the latter unnecessary.

The estimation of diastolic pressure by this method should be combined (as a routine practice) with the use of the auditory method for systolic estimation, checked by the ordinary tactile method—in order to confirm the validity of the auditory method as applied in any particular case. This combination we strongly recommend : also the use of local compression as an aid in doubtful cases (with resistant arterial walls, &c.), in the estimation of the systolic pressure.

Diastolic pressure estimation by the auditory method is not only as simple in application as the systolic estimation, but is comparatively little, if at all, influenced by many of the complications as regards local conditions, &c., which may in some cases introduce serious fallacy into systolic estimations ; it also causes less disturbance (circulatory, &c.), in very sensitive subjects, much less constriction of the limb being needed.

The pulse-pressure range as determined by the auditory method is much more extensive in many pathological conditions than is indicated by the ordinarily accepted ratios.

Changes in diastolic pressure of relatively small amount, unless dependent on an altered pulse-rate, are of much significance as indications of circulatory conditions.

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INTERPOLATED EXTRASYSTOLES, IN AN APPARENTLY NORMAL HUMAN HEART, ILLUSTRATED BY ELECTRO-CARDIOGRAMS AND POLYGRAMS.

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SINCE September, 1908, during the course of the routine physical examinations at Cornell University, we have taken occasion to study irregular hearts in otherwise healthy young men. In view of the fact that most of the irregularities reported are those of hearts damaged by disease or altered by advanced age, we have thought it worth while to devote considerable time to some in which the factors of demonstrable lesions and changes, incident to advancing years, are absent.

To those who have had the opportunity of examining large numbers of young persons it is well known that variations of cardiac rhythm are relatively frequent, and the fact has been noted that irregularities may be found in all gradations. It is of great importance that we learn more as to the cause and significance of abnormal contractions and whether cases often considered as functional disturbances do not in reality tend to become chronic.

The following case is selected because it is illustrative of a class lacking definite evidence of cardiac damage but with a history and constancy of altered beats suggestive of pathological lesion. Doubtless a borderline class exists in which ordinary activities are compatible with apparent health, but in which the ultimate course is towards cardia exhaustion.

*Historical Review.**

In the many published papers upon extrasystoles one finds but comparatively few specific references to the interpolated beat. Interest of physiologists in the extrasystole dates from the appearance, in 1876 and 1882, of Marey's classical works [1] on the circulation. In his tracings appear some examples of premature systoles followed by pauses not fully compensatory. In 1882 Dastre [6] published a work on the heart in which he maintained that extrasystoles without a compensatory pause came only in the ganglion free apex of the heart. This view was again brought forward by Kaiser [22] several years later. Prominent among the many physiologists who were stimulated to study the properties of heart muscle by the experiments of Marey was Engelmann,[11] whose work in 1894 on the compensatory pause perhaps first revealed clearly the possibility of interpolated extrasystoles.

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* The chronological review here given deals mainly with specific references to interpolated extrasystoles. The list of articles is as complete as we have been able to make it.

In 1899 Wenckebach[46](a) pointed out specifically that ventricular extrasystoles may occur in slowly beating hearts in such a manner as to lack a compensatory pause. His explanation was that after the extrasystoles the heart had partially recovered its irritability, by virtue of the slow rhythm, and consequently the normal physiological stimulus is effective. Wenckebach has on several occasions[46](b, c, d, e, f), referred to this type of irregularity and has expressed the opinion[46](e, p. 347), that it is not so rare as he at first thought. However, in his book on arrhythmia, he distinctly states that the interpolated beat occurs rarely. Mackenzie[31] makes a similar statement in his book on the pulse (1902, p. 103). He says, " Such pulses as these (i.e., those with extrasystoles without the prolonged pause) are extremely rare, and I cannot tell what the significance may be."

In 1903 Trendelenburg[42] began a systematic study of the subject. He cooled the sinus of the frog heart and stimulated the ventricle electrically, and was able to produce interpolated beats. Since this work such experimental extrasystoles have frequently been seen. Of the experimenters upon the mammalian heart Woodworth[45]* (1903) was one of the first to produce artificial interpolated beats. He used the isolated apex preparation of Porter and obtained ventricular extrasystoles with variable pauses, some of which were quite short. Three years later Erlanger,[11] in a paper on heart-block, showed tracings revealing extrasystoles with short pauses. Pan,[35] in 1903, described a case of extrasystoles in the human heart, some of the pauses being compensatory but some being undoubtedly short pauses of interpolated beats. In 1904 Volhard[43] published an article on " ventricular bigeminy without compensatory pauses." One of his tracings shows interpolated systoles. In this year Hoffmann[20] called attention to the fact that in paroxysmal tachycardia the pulse rate is doubled, nearly or exactly. This observation was confirmed, at least as regards approximate doubling of the rate, by Gerhardt,[13] Lommel,[29] Rihl,[38] Hoffmann[21] (in a second paper), and Hewlett.[15] It was assumed in these earlier papers of Hoffmann, Gerhardt and Lommel that the doubling was caused by the interpolation of extrasystoles midway between the regular beats. In 1905 Hering[16] wrote that he had observed interpolated beats in man with a pulse rate as high as 70 to 80, but never when the rate was higher. He stated that usually the pulse rate is slow and that interpolation occurs early in diastole. In various articles[17] on experiments with the mammalian heart he gives numerous examples of induced ventricular extrasystoles without the compensatory pause. In 1904, under the title " continual heart-bigeminy," he described a case[17](b) in which interpolated extrasystoles produced a pseudo-pulsus alternans. In 1905 further evidence of interpolated extrasystoles in the human heart accumulated. Rihl[39] produced them experimentally in the mammalian heart and Lichtheim[28] saw them in a case of Adams-Stokes disease. There is also some evidence of such extrasystoles in Finkelnberg's[12] tracings, but his curves are not very satisfactory.

Still another paper by Pan[26] in 1905 recorded a series of fourteen cases of extrasystoles, of which twelve were of the ventricular type. In three of these twelve interpolated beats occurred. Gibson's work,[14] in 1905, on bradycardia contained curves of interpolated extrasystoles, though he did not speak of them. In 1906 Wenckebach[46](e) called attention to these tracings of Gibson and to those of Vinnis,[44] pointing out that they contained interpolated systoles.

Mackenzie[32] in 1907 and 1908 gave further graphic records of these contractions, and in the two editions of his book,[33] 1908, 1910, again referred to them, giving tracings. In his second edition (1910) he again states (p. xviii) that the interpolated systole occurs rarely. In 1909 Hay[15] in his book illustrated in three figures, 59, 60, 61, this type of irregularity. He emphasised the lengthening of the a-c interval following the interpolated extrasystole in these instances. In the same year Cushny[8] during his work on aconitine saw this type of abnormal beat. Sometimes two beats were interpolated between two normal ones. Trendelenburg[42](b) showed that extrasystoles of the frog's auricle could be induced without disturbing the sinus rhythm. In 1910 Lewis[24] described a case of what he then believed to be interpolated auricular extrasystoles,† but in a later paper[24] (footnote) he concluded that the first interpretation as to their being interpolated was wrong. In his book[24] Lewis gives no additional cases, but refers to Laslett's article[22] in describing the mechanism of interpolation of ventricular beats. In this interesting case Laslett observed regularly recurring interpolated extrasystoles. A prominent feature of the case was the regularity with which the ectopic contractions occurred. It was a good example of allorrhythmia. More recently Staehelin and Nicolai[41] have reported a case of interpolated extrasystoles recorded by the string galvanometer. The heart was pathological, and was easily embarrassed by physical exertion. Vaquez,[4] and Pezzi and Sabri[37] have lately noted the interpolated beat. The last publications‡ to come to our notice are those of Busquet and Cushny. Busquet experimented with the chloride of magnesium and lithium and with pilocarpine, using

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† In Hewlett's case[19] of blocked auricular extrasystoles, cited by Lewis,[24] the auricular extrasystoles sometimes excited the ventricles, but often blocking occurred, due, Hewlett thought, to lowered conductivity of the His bundle. The sinus rate in this case was about 75. The pause following the abnormal beat was considerably shortened in some instances.

‡ Williams, H. B., Columbia University, has an unpublished case.

the heart of the frog and rabbit. His results were very interesting. Interpolated extrasystoles were frequently obtained, especially when the heart rate was slowed by the drugs or by subnormal temperature. More rarely interpolation occurred when the rate was normal. Busquet raises interesting physiological questions and points out that in instances of interpolation a number of factors must be involved.

Cushny[4] has recently studied the isolated mammalian ventricle with special reference to the development of spontaneous rhythm. In the course of his experiments he has observed a few interpolated systoles. An interesting fact, pointed out by Rihl[10] in connection with these interpolated systoles was that the first, or first and second, post-compensatory contractions following the extrasystole were increased in strength.

History.

T. is a Chinese student; age 25 years; weight 112 lbs.; physical condition good; has no bad habits. He uses tobacco very moderately, averaging two cigarettes a day. The family history is without bearing upon the present case, both parents, a sister, and two brothers being healthy. One brother died in childhood.

At the age of twelve he had an attack of "chills and fever," probably malaria. At nineteen, he was confined to his bed for two weeks with an illness characterised by a sore throat, fever, and evanescent, shifting joint pains. For an additional two weeks he was unable to walk and then began a very slow convalescence. Recovery was complete, as he thought, since he was not at any time aware of any unusual heart action. During this illness he was under the care of a Chinese physician who as far as we can learn did not make a diagnosis.

In September, 1910, he entered Cornell University and underwent the routine examination required of all students. During this examination, he learned for the first time that his heart was beating in an abnormal manner and expressed surprise, for he had always led an active life without signs of cardiac embarrassment.

Rather numerous subcutaneous nodules were observed on the arms and trunk, but with this exception and the heart findings he seemed to be normal. The impulse could be seen in the fifth interspace, slightly within the nipple line, and three and one-fourth inches from the sternum. The impact was plainly felt on palpation and was without thrills. On auscultating, sounds characteristic of extrasystoles were heard, thus: Lub-Dup, Lub-Dup-Lub, Lub-Dup, &c., the usual type being an extrasystole after each beat, or after each second beat, and less often after even more prolonged intervals. The semilunar valve sound accompanied the extrasystole in a fair proportion of the beats.

A soft, low-pitched murmur was audible in the apex region but was not transmitted; it disappeared when the breathing was suspended in expiration. It was doubtless accidental. A fluoroscopic examination confirmed our conclusion that there was no hypertrophy but it did not yield anything of value relative to the heart movements. The electrocardiograms of physiological beats were normal.

During the three years he has been under observation no additional signs have been recorded. Only in two instances has his heart been found beating without extrasystoles, once for a few consecutive beats and again for an entire afternoon, with the exception of brief intervals following severe exertion. Nervousness has been absent during the entire time of these observations.

Methods.

Polygraphic and electrocardiographic records have been made. In the ordinary way, tracings were taken simultaneously from the jugular bulb, from the carotid artery at the level of the lower border of the thyroid cartilage, and from the apex of the heart, the body being usually in the supine position. The recording and receiving tambours were, it is needless to say, connected by tubing of the same length and diameter. All of the records were made upon smoked paper, run by a Harvard long paper kymograph, as a rule. This apparatus permits at least nine metres of tracing to be made at one sitting, and the speed can be varied sufficiently to elucidate time relations. The time tracing was made by an accurately vibrating Bernstein spring interrupter, making 25, 30, or 50 contacts per sec.. For the purpose of accurately locating important points in the tracings ordinates were drawn by the levers and a pair of dividers served to mark the necessary distances.

For the excellent electro- and phonocardiograms reproduced, we are indebted to Dr. H. B. Williams, of the Medical School, Columbia University.

Fig. 1. A typical record of our series. The tracing begins with two normal beats, after which an interpolated extrasystole follows. The extrasystole is repeated five times and each time causes two more or less distinct waves in the phlebogram. (They are lettered arbitrarily "N" and "O.") At extrasystoles Nos. 1, 2 and 5 the waves N and O are doubtless c and a waves; at Nos. 3, 4 and 6 it is difficult to say what the wave O is.   Time in thirtieths second.   The heart rate is about 50.

Fig. 2. Made about ten months after Fig. 1.   There are apparently two extrasystoles between normal beats 1 and 2, 5 and 6, and 7 and 8.   This is the only record of the sort in the series.   Certain questionable waves in the cardiogram are marked by the "?." Between normal beats 7 and 8, the wave at ordinate 2 can not be an a.   The conduction time would be too long.

Description and discussion of tracings.

Tracings have been made under varied conditions.

As is usual in most hearts with extrasystoles, certain characteristic features are repeated from time to time. Fig. 1 and 2 are typical polygrams of our series. In Fig. 1 it may be seen that the dominant rhythm is quite regular, although several extrasystoles have occurred ; it is plain that they are interpolated. However, the interpretation of the jugular record is difficult, as close inspection of the figure will show (see the legend). In Fig. 2 the matter is further complicated by the apparent occurrence of double interpolations. While one might conclude from Fig. 2 that two extrasystoles have occurred between the normal beats, several electrocardiograms which have been made on two occasions did not reveal this phenomenon on those days.

In at first attempting to explain the type of phlebogram shown, several questions presented themselves : Were we dealing with regurgitation from the right auricle ? Why were the *a* waves absent, apparently, at certain points where they should normally occur ? Were the extrasystoles purely ventricular, or were they followed by retrograde auricular contractions ? Was it possible that nodal extrasystoles were occurring ?

We could not answer these questions satisfactorily until electrocardiograms were made. These we obtained on two separate dates, two, and two and a-half years, respectively, after our first observations of this case.

1. The possibility of regurgitation. A few remarks will suffice. Volhard (loc. cit.) and others have claimed that when extrasystoles occur there may be a back flow of blood into the auricle because of incomplete contraction of the *a-v* ring not permitting the valve leaflets to approximate perfectly. While admitting the possibility of this insufficiency, we have not been able to detect any evidence of it in the present case.

2. The omission of the *a* wave. It is shown by all of the electrocardiograms that the *P* elevation is never absent, unless it is obscured by the end of a preceding atypical complex. Moreover, the *P* elevations are regularly spaced, usually, and have a fairly constant height. Hence, the auricle always contracts, and with fair regularity. The absence of the *a* wave depends, therefore, upon the incomplete filling of the auricle and conduction of the contraction wave into the vein (see the last extrasystole, between normal beats 7 and 8, Fig. 2).

3. Retrograde contractions. Concerning the possibility of retrogression, physiologists are pretty well agreed that it may occur in the human heart. It is believed by some that when retrograde contractions take place the *Vs-As* interval exceeds the *As-Vs* interval (Lewis[25] p. 134). Williams[47] has reported an interesting case of reversal of the cardiac mechanism studied by means of the Einthoven galvanometer. He was fortunate in securing

on the same day records of reversed rhythm and of normal sequence.   On that day the *R-P* interval exactly equalled *P-R* and was 0·18 sec. in lead *II*.*

Bearing upon the possibility of retrogression in the present case, it is pointed out that the *P-R* interval, in all three leads, is distinctly lengthened, now and then, by the occurrence of a preceding extrasystole.†   Thus, in Fig. 4 the *P-R* interval at the systole *x* is 0·24 sec. and at *y* it is 0·18 sec.. This is to be taken as evidence of depression of the conduction system, but to what extent the depression extends towards the auricle cannot be stated. At any rate, there is no evidence that the stimulus excites the auricle.   In our polygrams mechanically recorded we were never certain of lengthened *a-c* intervals, and though the electrical records show actual depression of the conduction system, there has never been any further grade of heart block. Occasionally, of course, when a normal beat followed too soon after an extrasystole (see Fig. 6) there was no response.

4. Nodal extrasystoles are also ruled out.   The question whether or not such contractions could be interpolated has occurred to us.   So far as we can determine, they have not been observed by other writers.

The origin of the ectopic impulse and the course of the excitation wave.

The electrical complexes of any one lead are of very constant form. Two sets of tracings (see Fig. 4, 5, 6, 13, 14), made six months apart, were identical in essential characters, thus indicating that the origin of the stimulus and path of conduction are constant.   This is an interesting feature in the present case because of the probable long-standing of the irregularity.‡ In the light of the recent work of Einthoven, Eppinger and Rothberger, Lewis and others, it may be said that our electrocardiograms show the site of origin of the abnormal stimulus to be in the right ventricle, and probably in the right branch of the *A-V* bundle, for the general form of the atypical electrocardiograms is that of a systole resulting from a stimulus passing over the right branch of the *A-V* bundle only.

It is of course impossible to trace, except roughly, the path of transmission, but from the peculiar form of the atypical electrical curves we venture upon an interpretation.   The small height of the peaks in lead *I* indicates that the wave travels from base towards apex (Einthoven[7]).   The wave of negativity must at first have a transverse direction in the ventricles, for a systole of the left ventricle immediately follows that of the right. This sequence is proved by the distinct impulse in the carotid after many

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* Private communication.

† Stachelin and Nicolai (loc. cit.) state that the extrasystoles did not affect the *P-R* interval in the case that they reported, nor did it in other cases they had seen.   Pan and Gerhardt, on the other hand, observed lengthening of the conduction time.

‡ Lewis,[20] p. 152, has called attention to this character of heterogenetic stimuli, and in a paper[27] on the origin of premature beats has expressed the tentative belief that " the majority, if not all premature beats, arise in the special system of junctional tissues."   The same conclusion was expressed by Mackenzie[32] as result of his polygraphic studies.

of the ectopic beats.   Eppinger and Rothberger* have shown that when one ventricle responds to a stimulus from the other the delay is about 0·03 sec.. It is interesting and suggestive that the decreasing negativity of the base, represented by the descending limb of the initial upward deflection of the extrasystolic wave, is interrupted by a second upward deflection, producing the notch in the peak in lead *III*. This notch falls just about 0·03-0·04 second after the initial deflection and would seem to be due to the propagation of the wave of negativity to the basal part of the left ventricle. Immediately after this the negativity of the apex is developed (see leads *II* and *III*). A diagram similar to that of Einthoven, Fahr and de Waart[9] will be of help in this interpretation :
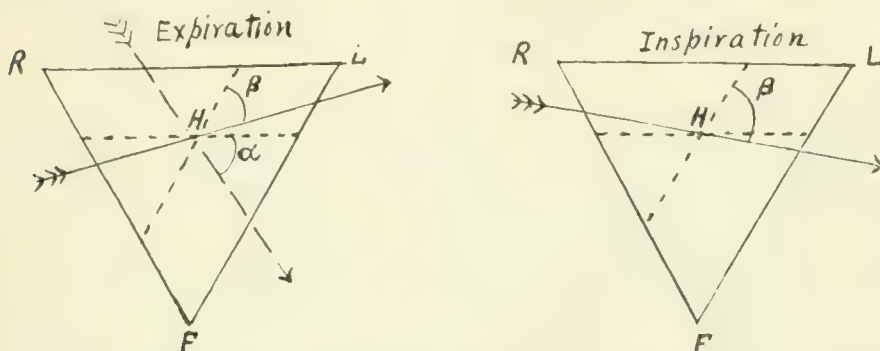
Fig. 3.   *R* corresponds to the right hand, *L* to the left, and *F* to the foot.   The heart is designated by H.   The solid arrow gives the assumed initial direction of the potential difference in the ventricles at an abnormal beat.   The letter β indicates the possible angle this direction of potential change makes with the direction of lead *III*, in expiration and inspiration.   The angle α in this figure is about 56°.   It gives the direction of the normal potential difference of the heart.†

If we are right in our conclusion as to the direction of this initial change of potential, we should expect that a displacement of the apex to the right would decrease, or perhaps abolish, the notch in question, providing the angle β in Fig. 3 could be made great enough, as in deep inspiration.   This is, in fact, what happens, for we see that in expiration the notch is well developed, while in deep inspiration it disappears. (See Fig. 7, 8.) In harmony with this explanation is the further fact that the notch is absent in lead *II*.   These leads give the resultant in the coronal plane, but it is to be remembered that there may be a component in the sagittal plane also ; we made no effort to study this possibility, and so cannot say to what extent it may be a factor in the form of the curve.

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* Zentralb. f. Physiol., 1910, 24, 1055.

† The angle α in Fig. 13 was calculated by the method of Einthoven, Fahr and de Waart[9] from the height of *R* in leads *I*, *II* and *III* of Fig. 4, 5 and 6. The values were : $R_{I}=9\cdot5$; $R_{II}=17\cdot6$; $R_{III}=8\cdot2$ tenths of a millivolt.   Einthoven's law[7] (p. 558), $R_{II}=(R_{II}-R_{I}=R_{III})$ holds good here : 17·6—9·5=8·1. As we did not record the respiratory movements in connection with the three leads in forced respiration, we cannot calculate accurately the amount of change in the angle α under that condition.

Abscissa, 1 division = ·04 second.
Ordinate, 1 division = ·10⁻⁴ volt.
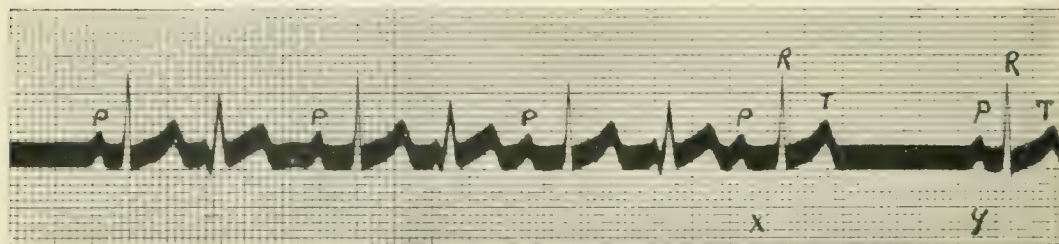
Fig. 4.   Fig. 4, 5 and 6 were made June the 28th, 1913. The character of the *E.K.G.* of this date is the same as of those made six months before (Fig. 13 and 14) except that in Fig. 4 (Lead *I*) one of the peaks of the extrasystole becomes decidedly more prominent (second upward deflection).   The final positive variation resembles closely a normal *T.* Note the difference in the *P-R* intervals at points *x* and *y.*
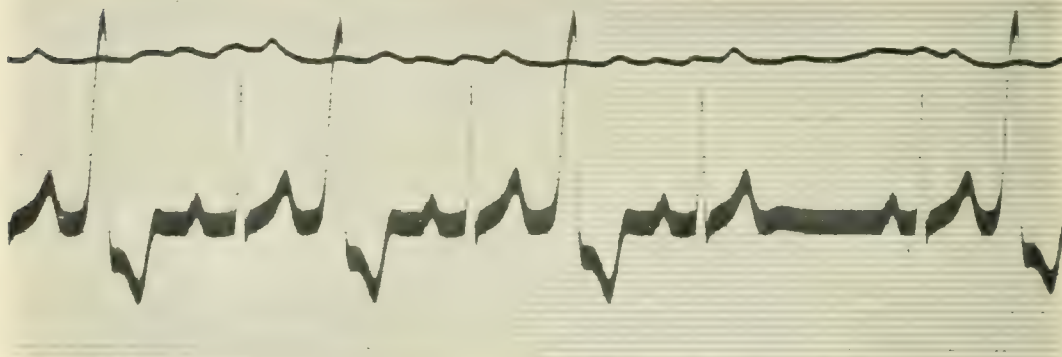
Fig. 5.   Lead *II*, June the 28th, 1913.
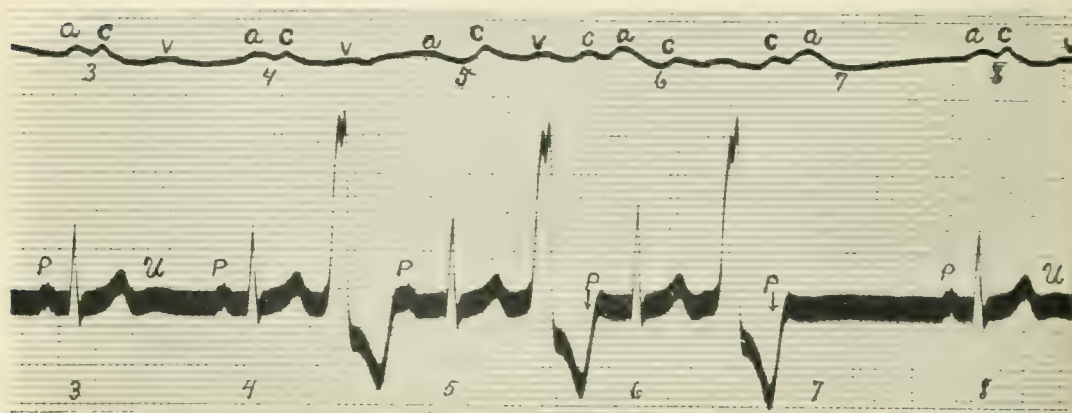
Fig. 6.   Lead *III*, June the 28th, 1913. A compensatory pause of the ventricle is shown between Nos. 6 and 8.   The pause results because the ventricle is still in systole when the auricular impulse reaches it.   That the auricle contracted is shown by the venous tracing. The *P* elevations are equally spaced.   At No. 6 a remarkable thing occurs, for it is seen that the ventricle responds, producing a normal *R S T*, even though the auricle had contracted before the extrasystole was finished. Also, whenever they occur, the extrasystoles follow the normal beats by practically the same interval   (a *U* wave is seen at Nos. 3 and 8).
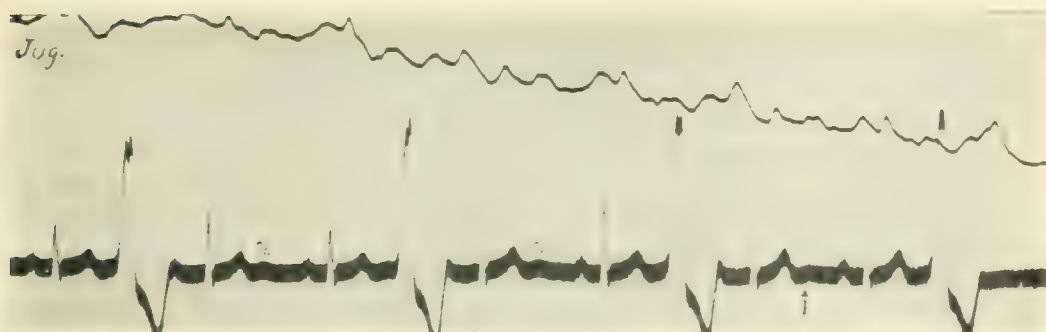
Fig. 7. Lead *III*. The effect of deep inspiration upon notched peak (see page 203). Forced inspiration reaches a maximum at the arrow. In this phase the notch disappears. (Two *U* waves are seen in this figure.)
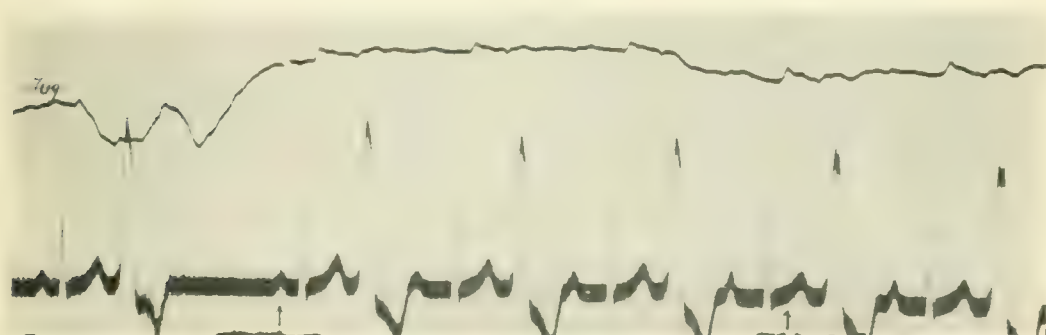
Fig. 8. Lead *III*. Deep inspiration, ending at the first arrow, is followed by expiration, which is well advanced at the second arrow. The notch returns in this phase.
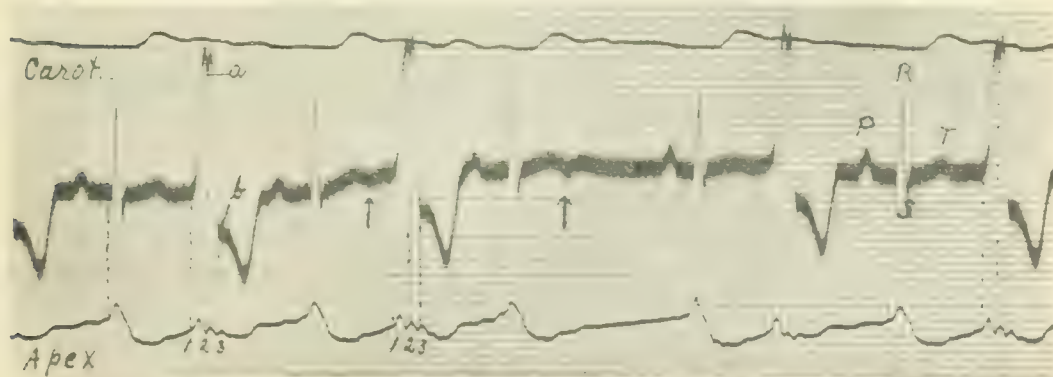
Fig. 9. The cardiogram has been moved to the left to bring its onset in line with the onset of the *E.K.G.* (Lead *III*). The three waves (1, 2 and 3) in the apical record of the extrasystole are synchronous with three points in the *E.K.G.*. It is suggested that the point *a* of the *E.K.G.* marks the onset of the systole of left ventricle. Note the negative and positive deflections following the *T* waves, at the points marked by the arrows.

In studying the relations of the electrocardiograms to the polygrams an interesting synchronism of certain points has been observed, and this has led to a plausible explanation* of the peculiar cardiograms in our tracings (see Fig. 1, 9, 12). In Fig. 9 the apex record departs most from the normal. In this figure the cardiogram has been moved to the left, so as to bring the onset of the abnormal beat, with its three waves, at the same ordinate that marks the onset of the corresponding electrocardiogram. It will be seen that the second part of the compound apex wave (1, 2, 3) is synchronous with a point a of the positive peak, and that the third wave of the cardiogram is synchronous with a point b in the negative part of the curve. These time relations lend support to the view that both the mechanical and the electrical tracings are expressions of asynchronous action of the ventricles, and that the point a marks the onset of the abnormal systole of the left basal portion of the heart.

We are inclined to believe, therefore, that the wave of negativity sweeps from a point in the basal portion of the right ventricle to the basal part of the left ventricle, and thence to the apex. That the right ventricle remains in systole longer than the left is to be inferred from the final upward deflection in lead I, this final wave resembling very closely a normal T^1. (Einthoven.[8])

The phonocardiograms (Fig. 10) are interesting in connection with the asynchronous action of the ventricles. They show that the second sound caused by an abnormal beat is sometimes divided, and that its duration then is about 0·03-0·04 second longer than the second sound of a normal beat. The first sound of an abnormal beat is also frequently about 0·04 second longer than a normal first sound.

As already stated, the compensatory pauses are rare in this heart. Fig. 6 shows a full pause, due to the impulse of the auricle falling in the refractory period of the ventricle. Fig. 8 shows one during inspiration only, and it is probable that the pause here is due to vagus influence. Fig. 6 is especially interesting because the fourth auricular contraction is not blocked, although it comes before the extrasystole is finished ; and we note further that the time relation between the normal and abnormal beats where the compensatory pause occurs is the same as at other points.

Attention is called to the effect inspiration has upon the normal and abnormal peaks. We omitted to make a special study of this matter, but in Fig. 7 and 8 it may be seen that deep inspiration markedly increases the height of the abnormal positive peaks, and that the R peaks undergo considerable variation, but in no regular way.

In closing this part of the paper, we may mention the assistance the electrocardiograms have given in deciphering the jugular tracings. Good examples are seen in Fig. 13 and 14.

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* We were at first of the opinion that the atypical apex tracings were really inverted cardiograms, produced by withdrawal of the apex from the chest owing to incomplete filling of the ventricle at the time of contraction.
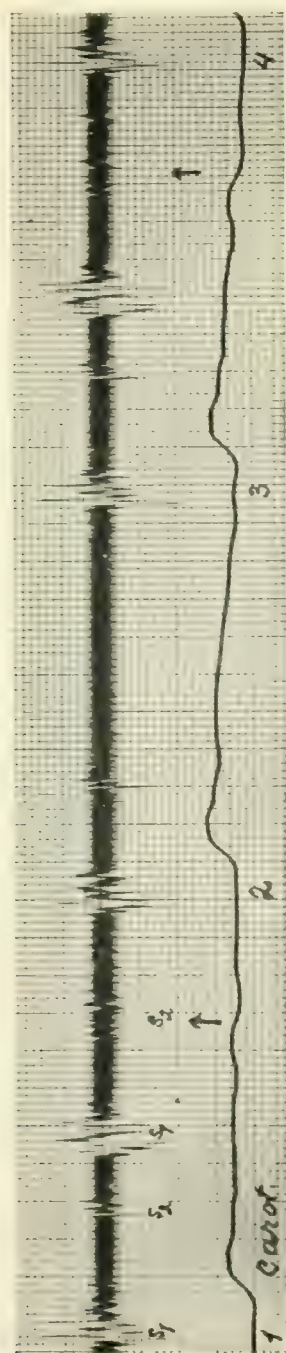
Fig. 10. A phonocardiogram. One abscissa div. = 0·02 sec.. s_1 marks the first sound ; s_2 marks the second sound. Both the first and second sounds of the extrasystoles are of longer duration than the corresponding sounds of the normal beats. The difference is about 0·04 second. At the points marked by the arrows the second sound of the extrasystole is divided. The interval between first and second sound is practically the same (0·32 sec.) at the normal and abnormal beats.

The effect of exercise.

TABLE I.

The effect of exercise upon the rate of the dominant rhythm, number of extrasystoles, total number of ventricular beats, and the interval between the normal and abnormal contractions.

Date of Observation.	Rate dominant rhythm.	No. of extrasystoles. *	Total No. ventricular systoles.	Interval between normal and extra-systoles.	REMARKS. (Apply to ventricular beats.)
1911 July 10	72	30	—	—	
July 12	92 86	44 30	88 86	— —	Immediately after long run. After resting few minutes.
July 13	60 92	few 32	—	15/30 sec. 13·5/30 sec.	Resting. Beats interpolated. After exercise. Beats premature.
July 20	60 120	55 50	110 120	13·2/30 sec. 12/30 sec.	Resting. Interpolated beats. After exercise. Beats premature
July 31	55	45	100	14/30 sec.	Resting. Interpolated beats.
Aug. 1	54 78	39 42	93 78	17/30 sec. 16/30 sec.	Resting. Interpolated beats. Exercise. Premature beats.
Aug. 7	50	36	74	17/30 sec.	Resting. Interpolated beats.
	100	50	100	16/30 sec.	Immediately after exercise. Beats premature.
	88	40 ?	88	—	Recovery. Beats premature.
	60	33	—	—	Rested. Beats interpolated.
Aug. 10	54	none	-	16/30 sec. (exercise)	Heart normal. Few interpolated beats after severe exercise.
1912 June 22	55 86 70	25 43 24	85 86 70	16/30 sec. 15/30 sec. —	Resting. Beats interpolated. Vigorous exercise. Beats premature. Recovery from exercise. Beats interpolated.
Oct. 3	56-60	39-45	105	—	Nearly every normal beat followed by extrasystole.

* Average number of extrasystoles 35 after rest ; 45 after exercise.

It will be noted that the rate of the dominant rhythm was influenced more by exercise than was the number of ectopic beats. The latter were undoubtedly increased, but not always to the same degree. It is interesting that on the day when extrasystoles were wholly absent (August the 10th) a few appeared after very strenuous exertion, but they soon disappeared. Another point is that they were just as frequent (44 per minute) on a day

when the normal rate of the heart was rapid (92, July the 12th), as on another day when the normal rate was slow (55, July the 31st). On August the 1st the number of extrasystoles was very slightly increased by exercise.

The question arises here as to the relation of the extrasystoles to the normal beats. Are the former called forth by the latter ? Is this a case of " bigeminy," in other words ? If we limit the term " bigeminy " to the accurate coupling of beats, as Lewis proposes[25] (p. 249), then this case would fall within the definition, for the extrasystoles have a pretty well fixed time relation to the normal beats. (They are separated by an average of 0·44 sec. in the electrocardiograms. Exercise tends to cause the extrasystole to come sooner after a normal beat than usual.) The galvanometric records show, however, that the normal and abnormal ventricular contractions have a different origin, so that in this sense they are not coupled. That the one is not dependent, absolutely, upon the other, is shown by the fact that the atypical beats often fail to develop.

Much experimental work is needed to aid in the solution of these problems of the extrasystole. In cases like the one here described the heart is probably damaged by the products of infectious disease, and it is possible that such conditions could be produced experimentally in the hearts of lower animals. Auer and Robinson[1] have shown that anaphylaxis can cause heart-block and ventricular ectopic beats, and it is known from clinical evidence that toxins of various kinds can so affect the heart as to disturb the function of stimulus production. We may expect to gain much additional information upon this subject from further work with the string galvanometer and other methods of study.

Resemblances to clinical tracings.

Fig. 11, taken just after a mile run, shows extrasystoles followed by full compensatory pauses. From the other records it is plain what has happened. In part A a premature beat of the ventricle follows every normal systole ; in part B, made five minutes later, the premature beat follows each second contraction. A pulsus bigeminus results, but not in the ordinary way. Here it is due to the failure of the extrasystole to force blood into the aorta. It is evident how different the interpretation would be if one would depend upon the sphygmogram alone.

In this connection we wish to call attention to the close similarity between certain of our arteriograms and those of pulsus alternans. The resemblance is only superficial, however, as can be seen by inspecting the phlebograms and electrocardiograms. A good example of the pseudo-alternans is shown in Fig. 13. In a sphygmogram alone the record would be deceptive, for sometimes this feature has extended over a considerable stretch of tracing. In Fig. 13 the pauses following the first two small beats (1 and 2) are actually shorter (as in true alternans) than the pauses preceding them, but at the points marked by the arrow the pause is too long for alternans.

This spacing is dependent upon the slow rise in ventricular pressure at the extrasystoles (see Fig. 12). We are reminded here that this delay, a common feature of extrasystoles, has been attributed by some solely to a weaker contraction of the heart muscle, but it is to be remembered that there are other factors influencing the speed with which the aortic valves are opened. They are the pressure in the aorta and the amount of blood in the heart. Both of these factors vary with the time elapsing after the normal beat. The earlier the extrasystole occurs the greater is the pressure in the aorta to be overcome and the less the amount of blood in the heart, and *vice versa*.
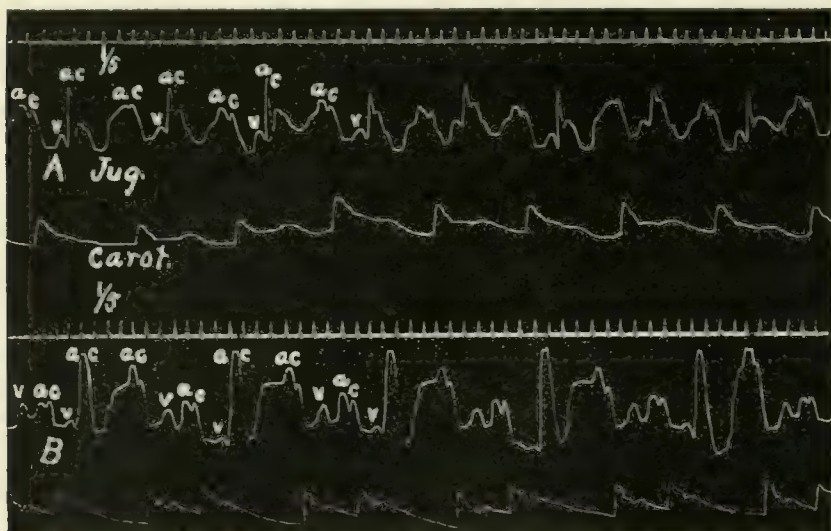
Fig. 11. The effect of exercise. Part A made after a mile run ; part B made five minutes after A. The extrasystoles and normal beats alternate in A ; in B every second normal beat is followed by an abnormal one, which fails to produce a pulse wave.

The onset of c.

Before closing this article we desire to call attention to a disputed time relation of the c wave and the carotid pulse.

In many of our tracings, it may be seen very frequently that the c wave is not synchronous with the carotid pulse wave.* In Fig. 12, which brings out this point clearly, the c wave precedes the carotid pulse wave by one-fifteenth second, in the second normal systole. The onset of the c wave in the third regular beat is uncertain. If we take it at the point marked by the "?," then the c wave begins one-tenth second before the carotid wave ; and if we refer to the extrasystoles, the difference in time is much more striking.

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* The jugular and carotid tracings were not taken at the same level in the neck, but a careful calculation shows that there could not be more than 1 90th, or at most 1 80th, second difference in time due to the difference in the level of the two tambours.
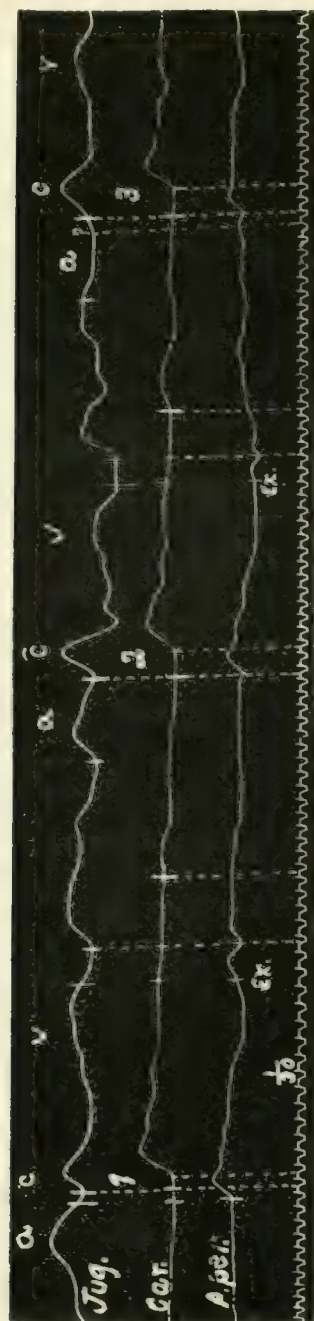
Fig. 12. The relation of the *c* wave to the carotid pulse. *c* precedes the carotid pulse distinctly, by as much as 1/15th of a second at No. 2. Extrasystoles occur at the points *cx*. The presphygmic interval is here much prolonged.

We have seldom found the two waves synchronous in this case. Our observations of these records convince us that the *c* wave is more nearly synchronous with the apex wave in the tracings described in this paper.
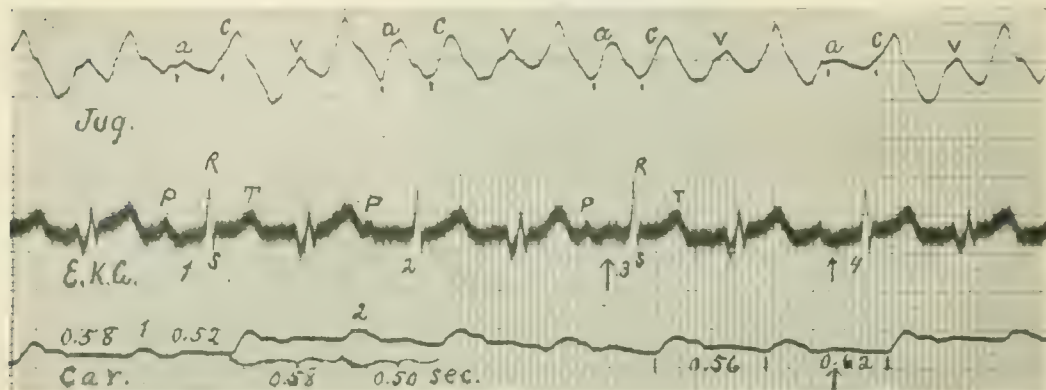
Fig. 13. Multiple tracing made December the 24th, 1912. Lead *I*. Abscissa, *I* div. = 0·04 sec.; ordinate, *I* div. = 10^{-4} volts. (These values are the same for all of the electrocardiograms.) The time of origin of the *a* and *c* waves, indicated by dots below the letters, has been calculated from the *E.K.G..* The phlebogram is very atypical. Note the pseudo pulsus alternans. The pauses are variable, but observe especially the length at Nos. 1 and 2 Notice the height of the *P* in the *E.K.G.*, and the extra positive wave between *P* and *R* of the third normal beat; at the fourth there is a negative variation between *P* and *R*; at the second regular systole there is slight evidence of fibrillation of the auricle. The disturbances are scarcely mechanical, or due to skeletal muscles.
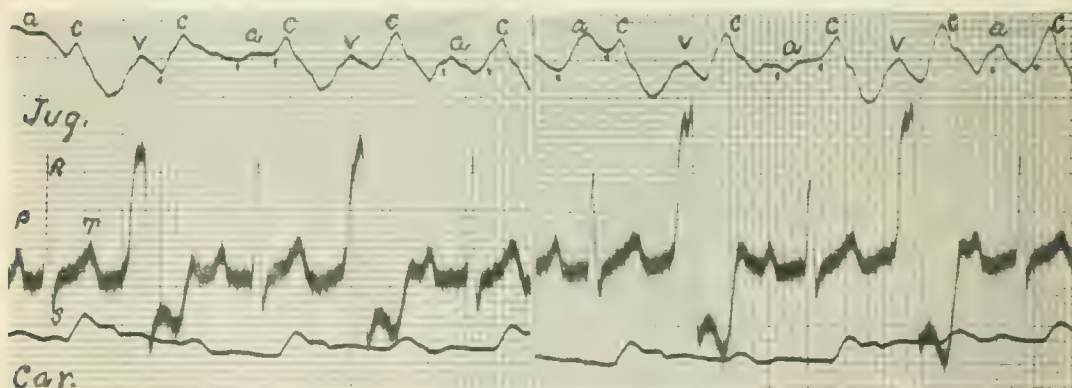
Fig. 14. Leads *II* and *III* (left and right portions of the figure). December the 24th, 1912.

It is not necessary to review the previous discussions about the origin of the *c* wave. That has recently been done by Bachmann[2] and Lewis.[28]* We wish simply to illustrate by Fig. 12 the fact that the *c* wave and carotid wave at the same level in the neck may be separated by a considerable

* See articles by Bachmann and Lewis for references to literature.

interval, which may not be apparent unless the record is made upon a rapidly revolving drum, as Bachmann has pointed out in his article (loc. cit.) in which he calls attention to the lack of synchronism between the two waves. We may add that not only in this case but in tracings from normal subjects we have seen this lack of synchronism.

SUMMARY.

A case of frequently recurring interpolated extrasystoles, of obscure history, in an otherwise healthy young man, is described. The condition is comparatively rare, especially in hearts without a demonstrable lesion. In pathological hearts it is also uncommon, but perhaps not so rare as formerly believed.

The extrasystoles produce an unusual type of phlebogram and cardiogram difficult of interpretation; they suggest the possibility of regurgitation from the ventricle, retrograde contractions, and even nodal extrasystoles. Galvanometric records show that none of these is the true explanation.

From the electrocardiograms it is learned that the ectopic stimulus arises at a fixed focus in the right ventricle, and probably in the right branch of the A-V bundle, and that the contraction waves follow a fairly constant path through the basal portion of the ventricles and thence to the apex. The irregularity has been remarkably constant during at least three years.

An interesting time relation between the E.K.G. and the apex record is shown. It is doubtless an expression of the asynchronous action of the ventricles. The phonocardiograms, showing divided second sounds at the extrasystoles, and prolonged first sounds, support this view. The degree of irritability of the focus initiating these ectopic beats seems to be somewhat variable, as once in a great while extrasystoles do not occur, the heart action being quite normal. Exercise increases the number of ectopic beats, but not markedly. The records have exemplified two important types of arteriograms, those of pulsus bigeminus and of pulsus alternans, both he result of the extrasystoles. At times a marked lengthening of the presphygmic interval occurs at the extrasystoles; it is ascribed to three causes. Occasionally the pauses following these beats have been variable; rarely they have been compensatory.

There is a distinct lack of synchronism between the c wave and the carotid pulse. The c wave must have, in this heart, some other cause than impact from the carotid artery.

In conclusion, we wish to thank Dr. H. B. Williams for the valuable aid he gave in making the electrocardiograms for us in his laboratory at Columbia University, and for suggestions concerning the interpretation of the records.

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THE RELATIVE SYSTOLIC DISCHARGES OF THE RIGHT AND LEFT VENTRICLES AND THEIR BEARING ON PULMONARY CONGESTION AND DEPLETION.

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IF, for even a few minutes at a time, the right heart pumps more blood into the pulmonary vessels than the left heart pumps out of them, congestion of the lungs must result. If, on the other hand, the left heart pumps out more than the right pumps in, an acute depletion of the lungs would be produced. It is wonderful, not that pulmonary congestion sometimes occurs, but rather that it is not a common occurrence. It is still more remarkable that a condition of pulmonary depletion, except as the result of exsanguination, is unknown either to physiology or to clinical medicine.

During health the two sides of the heart must propel exactly the same volume of blood per minute. As they execute the same number of beats their systolic discharges must therefore on the average be absolutely equal. And as the heart (that is the ventricle) is a somewhat shapeless muscular bag divided into two compartments which appear rather unequal in size, it is a problem to determine the nature of the adjustment by which the exact equivalence of their systolic discharges is effected.

The direction in which we must look for a solution of this problem is indicated, we believe, by the following observation. When an excised mammalian heart is perfused with Locke's fluid, it often happens that while the right ventricle beats vigorously the left remains almost quiescent in a state of contracture. During the past few years a number of investigations have been carried out in this laboratory showing the controlling influence of venous pressure in distending the heart during diastole, and thus determining the volume discharged in systole. The idea naturally presented itself that under the conditions of a perfusion experiment the lack of any pressure within the left ventricle during diastole would account for its inactivity.

Accordingly. the drip tube of a small glass funnel was passed through one of the severed pulmonary veins and through the mitral orifice down into the left ventricle. When a few cubic centimetres of fluid were poured into the funnel. a part ran down into the ventricle, and the mitral flaps closed tightly round the drip tube. If the top of the column of fluid in the funnel stood a few millimetres above the level of the mitral orifice. the left ventricle began in the course of a few seconds to expand and contract as actively as the right. As the pressure in the perfusion system tied into the aorta was

much greater than that in the funnel, the left ventricle at each beat drove its contents up through the drip tube, instead of out through the semilunar valves ; and during the diastolic relaxation it received the same fluid again. The crucial observation, repeated in many similar experiments, was that the amplitude of the stroke of the left ventricle was mainly governed by the height of the column of fluid in the funnel. With fairly high pressures in the funnel the left ventricle executed beats of a volume greater than any of which the right ventricle was capable at any pressure. When the column of fluid in the funnel was reduced below a certain amount, the amplitude of stroke of the left rapidly fell below that of the right.

We make no exclusive claim to the observation that in a perfused heart the left ventricle automatically adjusts the amplitude of its contractions during systole to the pressure with which it is distended during diastole. It is in fact a common practice in experiments of this sort in many laboratories to render the aortic valves incompetent, so that some of the perfusing fluid leaks into the left ventricle and distends it. So far as we are aware, however, the significance of such observations for the regulation of the volume of blood in the lungs has not previously been pointed out.

Theory of the cardiac regulation of the pulmonary blood volume.

Whenever any condition (*e.g.,* a rise of pressure in the systemic veins) increases the volume of blood pumped into the pulmonary vessels by the right heart, the rise of pressure in the pulmonary veins (corresponding to the column of fluid in the drip tube in the experiment above described) stimulates the left ventricle to larger strokes. So long as the left heart is capable (as we find that it normally is) of responding to even a moderate rise of the diastolic distending pressure by relaxations and contractions larger than any of which the right heart is capable, pulmonary congestion is effectively guarded against. In this respect the left heart acts somewhat like a dam of moderate height across the outlet from a reservoir. The pressure and the volume can go no higher than its top. It is only when an abnormally great pressure is involved in the distension of the left heart, as the result of injured valves or excessive tonus, that the top of the dam is so far raised as to produce pulmonary congestion. On the other hand whenever the output of the right heart is in any way considerably decreased, the left ventricle responds to the lower pressure in the pulmonary veins by a more than proportionally decreased stroke. Thus the lungs are never drained of their blood.

Most of the literature dealing with the volume of blood in the lungs treats of variations in the capacity of the pulmonary vessels under the influence of respiration and of the existence of a vaso-motor innervation. The conceptions of vaso-constriction and vaso-dilatation which hold true of a limb or a loop of intestine cannot without modification be applied to the lungs. The limb and the intestine each receive only a fraction of the total

blood stream, and this fraction may be increased or decreased by compensatory changes elsewhere even at a time when the stream as a whole is being varied in an opposite sense. On the other hand the entire blood stream flows through the lungs, all parts of which are alike ; and the heart, or rather as we shall show the right ventricle, and not the vaso-motor mechanism, is the metre of the total circulation. Our observations greatly lessen the functional importance which physiologists have generally assigned to direct vascular control (vaso-motor innervation) of the volume of blood in the lungs. Analysis of all of our data indicates that, if in the body the left heart has the same tonus and elasticity as in our experiments, the " effective pressure "* in the pulmonary veins can never rise much, nor for more than a few seconds at a time, above 80 mm. saline nor fall much below 50 mm.. Whatever influence variations of vascular tonus in the lungs may have must be produced through the responsive adjustment of the left heart. Thus vaso-dilatation in the pulmonary area by decreasing the pressure in the pulmonary veins will temporarily induce a decreased stroke and allow accumulation of blood in the lungs, while vaso-constriction by raising the pressure will augment the stroke and cause a decrease in the volume.

Method of experimentation.

The technique employed in our experiments is shown in Fig. 1. Excluding failures eight cats were used. The animals were not anæsthetised, as even a little ether weakens the heart for such experiments, but were killed by decapitation. Ligatures were placed on the pulmonary artery, azygos vein, and both venæ cavæ. The heart was then removed from the body, a cannula tied into the stump of the aorta, and the perfusion immediately begun. The fluid used consisted of equal parts of defibrinated sheep's blood and Locke's solution. In some of our earlier experiments it was found that the heart soon developed an excessive tonus, a sort of cramp or contracture, which decreased the extent of its diastolic relaxations and required an abnormally great pressure for the distension of the left ventricle. The rate of flow through the coronary vessels was also very small.

In order to increase the flow and to reduce the tonus of the heart to a degree allowing maximal efficiency the perfusion fluid was impregnated with half its volume of CO_2 gas. Oxygen was then bubbled through it until it assumed a bright arterial colour. The bottle containing this fluid (C) and also the jar of saline (E) in which the heart was immersed were both placed in a water bath (D) kept at about 36°, a temperature at which the heart

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* The term " effective pressure," as used by Henderson and Barringer, [1 and 2] is the force which fills the heart during diastole. It is the difference between the pressure in the veins or auricle and that in the intra-pleural or pericardial spaces. As the latter is negative by 20 mm. to 80 mm. saline, the actual pressure in the pulmonary veins would be only slightly greater than the pressure of the atmosphere in the alveoli. Occasionally the pressure in the left auricle is below zero, and the pulmonary veins within the lungs must be partially collapsed. These conditions are practically identical with those in the systemic veins near the heart (*e.g.* the jugular). Since this paper was sent to press Wiggers[3] has published observations upon dogs under conditions as nearly normal as possible in which he finds the pressures in the right and left auricles to be approximately equal.

beat about 100 times a minute. A pressure of 120 cms. of water was imparted to the perfusion system by means of the device shown at the right in the figure (A A[1])
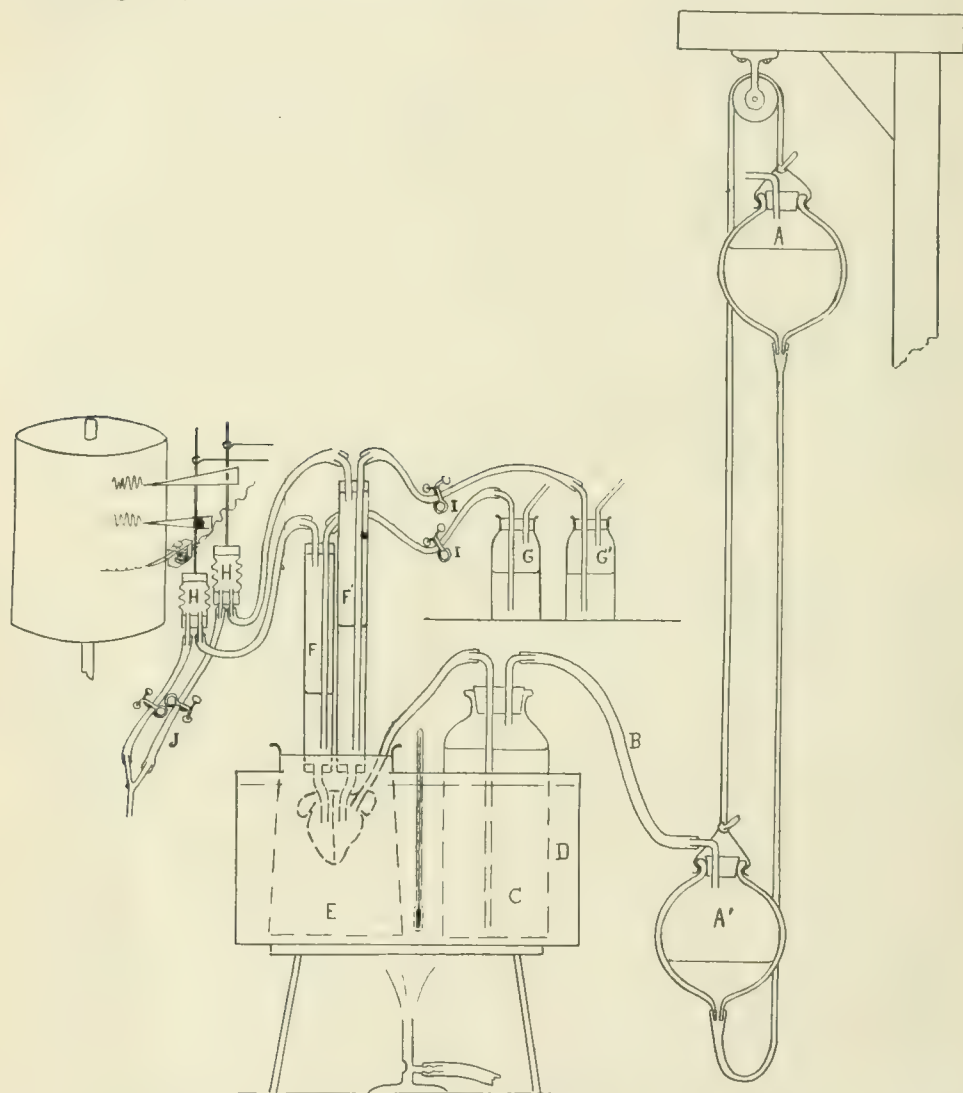
Fig. 1. Arrangement of heart and apparatus for recording the influence of various diastolic distending pressures in the right and left ventricles upon their amplitude of stroke. The pressure (120 cms. water) produced by AA[1] forces the perfusion fluid in C into the aorta of a cat's heart immersed in saline in jar E. Into the ventricles are inserted the cannulæ at the lower ends of the tubes FF[1], in which the amount of fluid can be varied by means of the bottles GG[1]. At each systole the ventricles force their contents up into FF[1], and during diastole receive the same volume again. The height of the columns of fluid in FF[1] above the surface of the saline in E is the diastolic distending pressure, and is measured by means of a millimetre scale (not shown). The amplitude of the pulsations of the columns, or volume of the systolic discharges, is traced on a smoked drum by means of the volume recorders HH[1]. When the volume in FF[1] is varied, the recorders are adjusted to an unchanged elevation by means of the tubes and clamps J.

The apparatus for producing the desired pressures in the ventricles consisted of two glass tubes (FF¹) of about 20 cms. length and 2 cms. diameter. In the lower end of each a brass cannula 5 cms. in length and 6·5 mm. bore was held by means of a perforated rubber stopper. On the left side of the heart the cannula was merely slipped in through one of the severed pulmonary veins and down into the ventricle. The closure of the mitral flaps around the cannula as soon as fluid was introduced entirely prevented leakage. On the right side the cannula was introduced through the vena cava superior and down into the ventricle. When very high pressures were produced, it was necessary to ligate the vein on the cannula, as the tricuspid valve was prone to be incompetent if the right heart was over distended. When the vein was thus ligated the perfusion fluid flowing from the coronary veins accumulated in the tube and gradually raised the column of liquid within it. Otherwise it escaped easily from the auricle through a severed vein.

The pressures within the ventricles were set at the desired values and varied by increasing or withdrawing the fluid in the tubes (FF¹). When the heart was beating vigorously the fluid sometimes pulsated as much as 10 or even 15 mm. rising as it was discharged from the ventricles during systole and falling as it ran back into them during diastole. The pressure causing each ventricle to fill was taken as the mean height of the top of the pulsating column, measured by means of a millimetre scale, above the surface of the fluid in the jar in which the heart and lower ends of the tubes were immersed.

The tubes were carefully tested to determine whether, under such heads of pressure as were used in our experiments and in a period of time equal to that of diastole, they were capable of delivering from the cannulæ at their lower ends volumes considerably greater than the tidal volumes of the ventricles actually observed. It was found that at low pressures the possible delivery of the tubes was 50 per cent., and at high pressures 100 per cent. greater, than either ventricle accepted in any of our experiments.

The volume recorders (HH¹) by means of which the amplitude of the pulsations in each tube was traced on a smoked drum were constructed of thin rubber finger cots, with a bit of cork in the upper end carrying a vertical straw as a guide. The lower ends were drawn over perforated rubber stoppers held by clamps and connected by tubing with the tubes (FF¹). These simple devices were found to be extremely quick in action, having an internal pressure of only 6 mm. water, and to be sufficiently accurate to record down to 0·2 c.c. the volume of the pulsations of the ventricles.

The relations of distending pressures to tidal volumes.

An example of the graphic records obtained is reproduced in Fig. 2. The upper curve expresses the activity of the right ventricle, and the lower that of the left. Below the time line are noted the " venous " or diastolic distending pressures. The relations of the curves and pressures are shown diagrammatically in Fig. 3. Here, and in Fig. 4 and 5, the broken lines
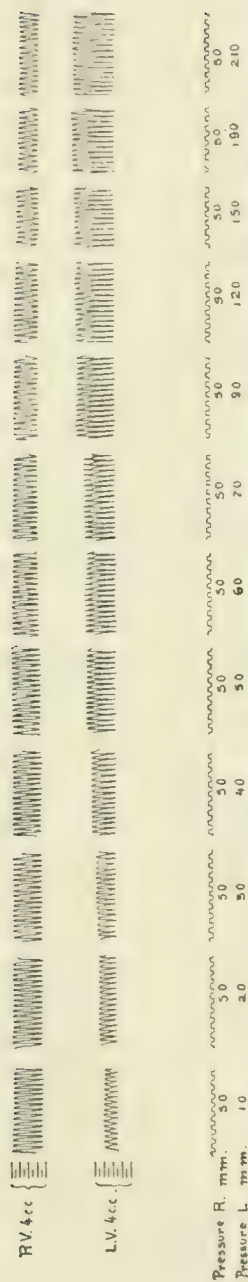
Fig. 2. About one-half original size. Volume curves of the right and left ventricles. Time in 0·5 seconds. The tidal volumes of the beats are determined by means of the scales at the left. The numerals below the time line give the height of the columns of fluid in the tubes (FF¹ in Fig. 1) causing the diastolic distension of the ventricles. The data obtainable from these curves and measurements are shown diagrammatically in Fig. 3.
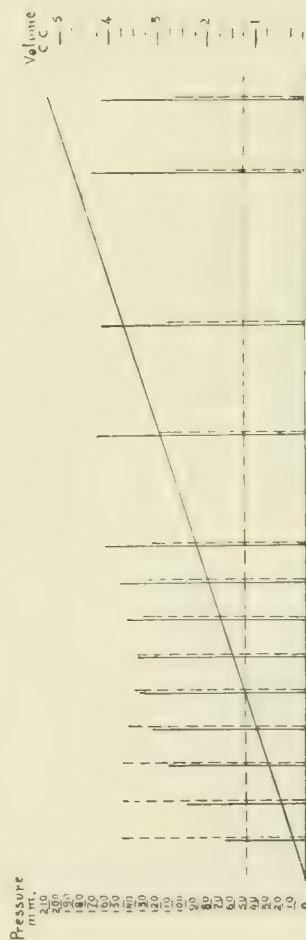
Fig. 3. Diagram of data obtained from Fig. 2. Broken lines refer to the right ventricle and unbroken to the left. Pressure scale in mm. saline at the left and volume scale at the right. The horizontal and sloping lines indicate the distending pressures in the ventricles. The paired vertical lines express the tidal volumes of the ventricles, at the pressures indicated by the height at which they intersect the pressure lines. The diagram shows that the pressure in the right ventricle was kept at 50 mm. throughout, while that in the left was increased gradually from 0 to 210 mm. At low pressures the tidal volume of the left is much less than the right, but equals it at about 50 mm. With further rise of pressure in the left its stroke continues to increase, although less rapidly, up to a maximum at 170 mm., while the right ventricle is so far interfered with by the great distension of the left that its tidal volume is decreased by nearly one-third.

refer to the right ventricle and the unbroken to the left. The paired vertical lines express the tidal volumes of the ventricles at the pressures indicated by the height at which they are intersected by the two pressure lines. The abscissa has no particular time value, except that a minute or two elapsed after each change of pressure, in order to allow the heart to become adjusted to the conditions, before the observations were taken.

In this experiment the pressure in the right ventricle (the horizontal line) was maintained throughout at 50 mm.: the "critical" level at which, as our other experiments show, and as Henderson and Barringer[1] found for the dog's heart also (confirmed by Piper[2]), the right ventricle attains maximum efficiency. The pressure in the left heart (the sloping line) on the contrary, starting at zero, was gradually increased. The smallness of the strokes of the left ventricle as compared with those of the right, as long as the pressure in the former was below that in the latter, shows the behaviour of the heart by which during life pulmonary depletion is prevented. Just beyond the point at which the two pressure lines intersect (*i.e.*, 50 mm. on both sides) the tidal volumes of the two ventricles are equal. Such equivalence during life would maintain the pressures in the pulmonary veins at practically the same amount as in the systemic veins near the heart,* and would keep the pulmonary blood volume constant.

As the pressure in the left ventricle was increased above 50 mm. the amplitude of stroke was still further augmented, although in lessening degree up to 170 mm.. The "critical" value thus indicated for the pressure in the pulmonary veins, *i.e.*, the pressure in response to which the left ventricle would respond with a maximum efficiency, is more than three times as great as that for the right heart and much greater than we have any reason to suppose ever occurs in the healthy body. From these observations it appears that during normal life the left ventricle (unlike the right) is seldom or never worked to its maximum efficiency. It is this margin of safety which insures the lungs against congestion.†

As the pressure in the left ventricle was increased above that in the right, not only was the tidal volume of the former augmented, but that of the latter was decreased. In life such conditions would occur when the left heart is over-loaded, and as a result the efficiency of the right ventricle impaired, and the blood stream dammed back in the systemic veins. There seems to have been no explanation heretofore as to how a systemic venous

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* Compare footnote on page 219.

† This property of the left ventricle affords a possible explanation for the slight respiratory variations in arterial pressure which sometimes occur even when the heart rate is uniform. The effective distending pressures in the right heart are generally increased by inspiration and decreased by expiration. On the other hand the different phases of respiration influence the capacity of the pulmonary vessels so that the effective pressures in the left heart are sometimes greater during expiration than during inspiration (Wiggers[4]). The tidal volumes discharged into the aorta are correspondingly augmented or lessened. The variations of arterial pressure thus induced (*i.e.* expiratory rise and inspiratory fall) are, however, usually so slight as to indicate no considerable deviation from the principle of the "superimpossibility of the volume curves." We believe that Henderson and Barringer[1] were correct in claiming that the right ventricle, owing to its low critical distending pressure, ordinarily works at full efficiency; and that in general variations in the heart rate are the cause of nearly all of the more considerable changes of arterial pressure synchronous with respiration.

engorgement can result from pulmonary congestion, except that the pressure in the pulmonary arteries is raised so high that the right ventricle is unable to make a full systolic discharge against it. The behaviour of the heart here noted suggests that the congestion may sometimes be, so to speak, short-circuited through the heart itself by displacement of the interventricular septum during diastole. There is ample experimental evidence to show that under all ordinary conditions the right heart discharges efficiently against any pressure that ever occurs in the lungs, and that its tidal volume is as completely independent of pulmonary resistance as it is entirely dependent upon the supply and pressure from the systemic veins.
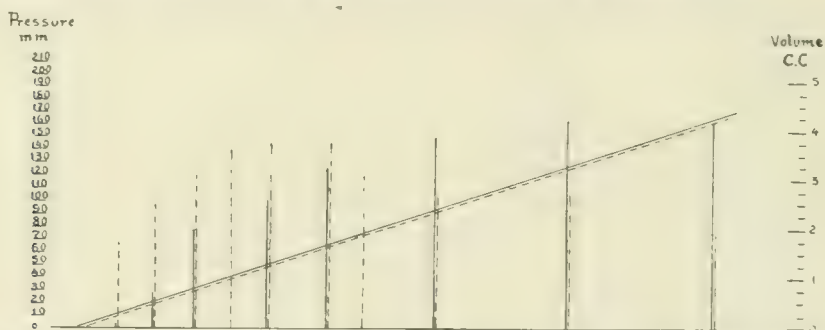
Fig. 4. Diagram of an experiment in which the pressures were increased simultaneously and equally. At first the tidal volumes of the right heart are considerably greater than those of the left. The former reach their maximum, however, at about 50 mm., and thereafter decrease notably while the latter continue to augment with increase of pressure.

Fig. 5. Diagram of an experiment in which the pressure in the left ventricle was maintained throughout at 80 to 90 mm., while that in the right was progressively increased. The critical pressure in the right is reached at about 50 mm., although the left (at 90 mm.) is still slightly more efficient. When the pressure in the right exceeds 70 mm. the strokes of both ventricles are noticeably decreased.

In Fig. 4 are shown diagrammatically the efficiency of the two sides of the heart in an experiment in which the pressures were increased simultaneously and equally. At the lower pressures the tidal volumes of the right greatly exceed those of the left. Under such conditions in the body blood would rapidly accumulate in the lungs. The critical pressure for the right was reached at 50 mm. At pressures above 70 mm. the right exhibits a marked decrease in stroke, while the left continues to increase up to 150 mm.. The pressure at which the two ventricles would pump the same volume of blood,

and thus keep the pulmonary blood volume constant, was in this case therefore about 70 mm., a pressure somewhat higher than in most of our experiments and due to the tonus of the left ventricle. At all pressures above this level the left heart, if it behaved in the body as under the conditions of the experiment, would pump out of the lungs a considerably greater volume that the right pumps in.

In Fig. 5 is shown the behaviour of the heart in an experiment in which the pressure in the right ventricle was gradually raised, while that in the left was kept at 80 to 90 mm.. At all times the tidal volumes in the left exceeded to a greater or less extent those in the right. The latter reached its critical pressure at about 50 mm.. Pressures in the right above 70 mm. caused a marked decrease in the amplitude of stroke in both ventricles. From this observation it appears that unusually high venous pressures, instead of augmenting the efficiency of the heart, may seriously interfere with its activity.

The whole mass of data obtained in all of our experiments was in such close agreement with the foregoing illustrations that it need not be further detailed. The method of observation was, as we fully realise, highly artificial and needful of corroboration along other lines. It has, however, the advantage of extreme simplicity and of affording so far as it goes a complete picture of the relations of the tidal volumes of the ventricles to each other and to their diastolic distending pressures. Moreover the behaviour of the ventricles under the conditions above described seems to us to throw some light on the manner in which the heart becomes adjusted to long continued conditions as defined by Sahli's laws.[3] In the course of these and other investigations on closely related topics we have in fact been frequently impressed with the idea that not only in the compensation of valvular defects, but also in the growth of the heart during childhood and in athletic training, the pressure in any one of the heart's chambers during diastole must be the principal factor determining its capacity and tidal volume, and the pressure during systole must be the factor regulating the thickness of its walls and the resistance which they are able to overcome when contracting.

Conclusions.

The experiments here reported show the controlling influence of the diastolic distending pressures in the ventricles upon their tidal volumes. The results indicate that the volume of blood in the lungs must be in great part regulated by the relative efficiency of the two sides of the heart.

The right ventricle (of the cat's heart) reaches its greatest tidal volume at the " critical " pressure of about 50 mm. saline. As this is approximately the effective pressure (*i.e.*, the absolute venous pressure plus intra-pleural negative pressure) maintained during life, the conclusion is drawn that the right ventricle normally works at maximum efficiency.

The left ventricle at pressures below 50 mm. saline has a much smaller stroke than the right. During life this function of the left ventricle prevents pulmonary depletion. Between 50 mm. and 80 mm. the two ventricles have about equal tidal volumes, and the volume of blood in the lungs therefore would be maintained at a nearly constant point. At higher pressures, the tidal volume of the left ventricle continues to increase up to a limit which is probably above any which occurs normally. This ability of the left ventricle, under high pressures in the lungs, to pump more than the right is the function which normally prevents pulmonary congestion.

The inference is drawn that during health the pressure in the pulmonary veins can never rise to much more than 80 mm. saline, nor fall to much less than 50 mm., above the (negative) pressure in the intra-pleural and pericardial spaces. These figures are not, however, invariable, but depend to a marked degree upon the tonus of the left heart, and, of course, upon the integrity of the valves. Other things being equal, the volume of blood in the lungs must vary as the tonus of the left ventricle.

High diastolic distending pressures in the left ventricle markedly interfere with the efficiency of the right. Over distension of the right may decrease the efficiency of both sides.

The behaviour of the heart in these experiments lends support to Sahli's laws of compensation, and suggests that these principles may apply also to the development of the heart in childhood and in athletic training.

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EXPERIMENTS ON THE ORIGIN AND PROPAGATION OF THE IMPULSE IN THE HEART.

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III - THE EFFECT OF VAGAL STIMULATION ON THE LOCATION OF THE PACEMAKER, THE LOCATION OF THE PACEMAKER IN AURICULO-VENTRICULAR RHYTHM, AND THE EFFECT OF VAGAL STIMULATION ON THIS RHYTHM.

Introduction.

It has been known since the work of Engelmann[4] and Lohmann[16] that under certain conditions the seat of impulse formation in the heart might shift, temporarily or for a longer period of time, from its normal position somewhere near the mouths of the great veins. These conditions have fallen into two classes : first, those which depress, eliminate, or block the influence of the sinus region ; and, second, those which exalt the activity of some other part possessing inherent automaticity. Since the discovery of specialised tissue in the mammalian heart, studies along this line have largely resolved themselves into investigations of the relations existing between the sinus and auriculo-ventricular nodes. A brief review of the past observations may serve as an introduction to our own work.

Engelmann[4] first clearly described what is now known as atrio-ventricular or nodal rhythm. In frog hearts after the first ligature of Stannius he found that in certain experiments the auricles and ventricle beat simultaneously, or nearly so. On the assumption that excitation spread in all directions at the same rate, Engelmann worked out on a mathematical basis where the impulse must have arisen to fulfil the time values of the *As-Vs* intervals. The point of origin was found to be the ventricular side of the auriculo-ventricular ring.

A year later Lohmann[16] observed that the spontaneous beats which broke through vagal inhibition both in the rabbit and the tortoise often showed a greatly reduced *As-Vs* interval. He located the seat of impulse formation in the " Brückenfasern " connecting auricles and ventricles. Accordingly as the ventricular, middle, or auricular portion of these structures became automatic the *As-Vs* intervals were negative, zero, or positive in value. By stimulating the auriculo-ventricular junction he produced a condition in which the intervals were permanently shortened. So far as we are aware this was the first time auriculo-ventricular rhythm had been produced experimentally in the mammalian heart.

Mackenzie[18] in 1904 described a clinical case in which the *a-c* interval of the venous pulse was zero. He believed that the auricles and ventricles were beating simultaneously but made no attempt to localise the point of impulse formation. Hering[9] in 1905 showed that accelerator stimulation might reduce the interval between auricular and ventricular systoles, and shortly afterward he secured a few auriculo-ventricular beats on vagal stimulation.

Lohmann[17] in 1908 extended his previous work by killing the sinus region with formalin. Auricles and ventricles soon beat synchronously. Since a ventricular extrasystole showed the normal delay on its passage to the auricle he reaffirmed his previous conclusion that the impulses were arising in the musculature of the auriculo-ventricular ring. Hering[10] repeated these experiments and confirmed them, adding the observation that in the early stages the pacemaker might apparently shift back and forth between the sinus region and the auriculo-ventricular border.

Hering[11] also tested the original proposition of Tawara that there might be a delay of conduction in the auriculo-ventricular node. He found this to be the case, the latent period of the auricle being twice as long when stimulated through the conductive system as when stimulated directly. The different values which the *As-Vs* intervals might have Hering sought to explain by assuming impulse formation in various parts of the auriculo-ventricular node. In this explanation he followed the suggestion previously made by Lohmann.

Rothberger and Winterberg[19 & 20] have published important papers on the relation of the cardiac nerves to atrio-ventricular autonomy. They found atrio-ventricular rhythm produced in 30 per cent. of their experiments by stimulation of the left accelerator nerve. The explanation of this they believed to be in the manner of nervous distribution, the left accelerator going almost exclusively to the auriculo-ventricular border. Simultaneous stimulation of the right vagus should have aided in bringing about this result, but practically it did not prove very effective.

Ganter and Zahn[8] secured atrio-ventricular rhythm by cooling the sinus with specially devised thermodes. During this rhythm changes in temperature were ineffective except when the thermodes were applied to that part of the auricular septum comprising Tawara's node. Brandenburg and Hoffmann[2] confirmed the previous experimenters and, in addition, found that if the sinus were extirpated by some method which caused great stimulation, such as cutting or clamping, an electrocardiogram resulted which was in all particulars like the normal. No part of the auricle could then be found in which cooling influenced the heart rate. Brandenburg and Hoffmann concluded that in these cases the seat of impulse formation had become diffuse in the auricular musculature.

In a recent paper Zahn[23] has sought to study the different portions of the auriculo ventricular node by means of his thermode method. He found that in atrio-ventricular rhythm induced by extirpation of the sinus region

with intense stimulation, as well as in those cases in which the *As-Vs* interval approached the normal value, the only part of the auricle in which cooling influenced the rate was that part of Tawara's node which extends towards the coronary sinus. When the interval was zero it was the middle portion of the node which was affected by cooling and in the case of negative intervals it was the ventricular portion alone which was influenced by temperature changes. In all cases Zahn believed the seat of impulse formation resided in some part of the specialised heart tissue.

Kuré[14] has also recently reviewed past work and studied carefully the effects of stimulation of the cardiac nerves on heterotopic impulse formation. Stimulation of the cardiac nerves by natural means such as asphyxia was shown to produce atrio-ventricular rhythm. The work confirmed that of Rothberger and Winterberg.

As a net result of the researches mentioned above we know that various procedures which depress, injure or extirpate the sinus node, such as cooling, cutting, clamping, burning and poisoning with certain drugs, or those procedures which stimulate the auriculo-ventricular junction such as left accelerator stimulation, will bring on a condition in which the *As-Vs* intervals are shortened, in some cases even becoming negative. The belief that in these cases the impulses are arising in the auriculo-ventricular node rests on deductions from the rate at which the excitation spreads over the heart, the delay in conduction found by Hering in Tawara's node, and the findings of Ganter and Zahn that heat or cold only affect the heart rate when applied to some part of the auriculo-ventricular node. The latter evidence, if confirmed, amounts to a demonstration of the correctness of the theory.

It has seemed to us that new light might be cast on these subjects by means of electrical studies. Our problem has therefore been to study by means of the principle of initial negativity the seat of impulse formation during vagal stimulation, the origin and course of the excitation during auriculo-ventricular rhythm, and the effect of vagal stimulation on this rhythm.

Methods.

The methods employed in this research have been similar to those described in the first paper of this series.[7] Initial negativity has been determined by connecting two parts of the heart through a string galvano-meter and noting the first movement of the shadow of the thread. This is the method which has been previously used by Wybauw,[22] Lewis[15] and others. Non-polarisable electrodes were fastened to the heart by means of woollen threads at the following places : No. 1, on the sulcus terminalis about 3 mm. below the angle of the superior vena cava and the right auricular appendage : No. 2, on the atrium of the right auricle about 6 mm. to the right of the sulcus terminalis ; No. 3, on the superior vena cava at about 10 mm. distance from the sinus electrode ; No. 4, on the coronary sulcus as near as possible to the ventral margin of the coronary sinus ; No. 5, on

the auricular septum just above the middle cusp of the tricuspid valve. The latter contact was secured by means of a long glass electrode passed through the external jugular and superior vena cava into the right auricle.

The position of the electrodes was always verified after the experiment and, in many cases, histological examinations were made. Electrode No. 1 was placed, as near as we could judge, on the head of the sinus node. The histological examinations proved that it was always at least in contact with nodal tissue. In placing Nos. 4 and 5 we attempted to bring them in contact with the different parts of the auriculo-ventricular node. The work of Aschoff[1] has shown that this node consists of a ventricular and an auricular portion, the latter sending processes around the coronary sinus. Our electrodes were thus at the extreme ends of this node. The coronary sinus electrode may not always have been directly on nodal tissue but it was always in very close relation to it, so close that we believe it must have expressed the electrical condition of this part.

The five electrodes just mentioned were attached to the galvanometer through a special key by means of which any two electrodes might be instantly connected. The following couples could in this way be compared at any moment :—

> Right auricle and sinus node.
>
> Right auricle and the ventricular part of the auriculo-ventricular node.
>
> Sinus node and the ventricular part of the auriculo-ventricular node.
>
> Sinus node and the superior vena cava.
>
> Ventricular part of the auriculo-ventricular node and the superior vena cava.
>
> Ventricular part of the auriculo-ventricular node and the coronary sinus.
>
> Superior vena cava and the coronary sinus.
>
> Superior vena cava and the right auricle.
>
> Coronary sinus and the right auricle.
>
> Coronary sinus and the sinus node.

The electrodes were so attached to the galvanometer that the upstroke on the photographic record indicated primary negativity in the second member of the couple. A mechanical record of the right auricle was also secured on the photographic record by means of air transmission and a tambour lever in front of the photographic slit. Simultaneously with the electrical records mechanical curves of the right auricle and right ventricle were secured on a smoked kymograph by air transmission. Wherever *As-Vs* intervals are mentioned, they refer to measurements from these records. This method of taking two sets of records at the same time proved invaluable. It gave the greatest possible information and made the

interpretation of extrasystoles and dropped beats either in the auricle or ventricle much more exact and certain.

Owing to difficulties in compensation it was found impracticable to secure records from all ten positions during the same period of vagal stimulation. Furthermore, the effect most desirable for study often appeared only for a few beats and, in such cases, changing from one position to another obscured the results. Each lead was therefore adopted separately and a continuous record made from just before the procedure until the normal rhythm was again regained. A long roll photographic recording apparatus made such records possible. The obvious disadvantage was that the heart would not always respond in the same way ten times successively. This difficulty we have tried to overcome by the large number of observations made.

All the experiments were carried out on dogs' hearts *in situ*. The animals were morphinised and the chest opened under ether anæsthesia with artificial respiration. By means of warmed air and hot water bags the body temperature was kept at or near the normal. In one experiment, No. 32, atropine was given to rule out the possibility that the changes in pacemaker in the experiments involving injury of the sinus region were due to stimulation of vagal fibres.

The origin of irregularities during vagal stimulation.

It has long been known that on vagal stimulation irregular beats of various kinds may appear. These have been studied particularly by Hering[13 & 21] and his students. Three types have usually been distinguished ; namely, auricular, atrio-ventricular and ventricular according to the place in which the impulse is supposed to have arisen. The proof that beats have had an ectopic origin in the auricle is a difficult one. The As-Vs interval is however, generally longer than that of the last preceding normal cycle. Rothberger and Winterberg[20] thought to determine it by the character of the P wave of the electrocardiogram. Beats arising in the auriculo-ventricular region have been identified by the As-Vs interval or the a-c interval of the venous pulse. According to Hering's observation[10] that delay in auriculo-ventricular conduction takes place only in Tawara's node any cycle with an As-Vs or an a-c interval less than normal must have arisen in some part of the auriculo-ventricular node. Ventricular extrasystoles would, therefore, have a Vs-As interval equal to or longer than the normal As-Vs.

In all experiments there are apt to be a large number of systoles in which the As-Vs interval closely approaches normal and an accurate designation of the origin of the beat becomes well-nigh impossible. Kuré's data[14] contain illustrations of this point. In one case the interval was reduced from ·10 sec. to ·08 sec.. The cycle was interpreted as atrio-ventricular yet it would seem quite possible that such differences might

depend on changes in conduction time. It was in order to demonstrate beyond question the origin of such beats that we have placed electrodes on various parts of the auricle and used the method of initial negativity.

The work of Wybauw[22] and of Lewis, Oppenheimer and Oppenheimer,[15] which we have repeatedly confirmed, has shown that in the normally beating heart the primary point of negativity is always in the upper part of the sulcus terminalis immediately over the sinus node. In determining the point of origin of irregular beats during vagal stimulation a comparison of this region with others was of primary importance. If beats were arising ectopically, the sinus node electrode would cease to be negative and become positive to the new point of impulse formation.

In twenty-seven experiments we have compared various parts of the right auricle with each other during vagal stimulation. Many of these showed no irregularities for certain leads but a sufficient number gave results which we believe justify certain conclusions. Results from the most important leads will be given briefly.

Sinus node and right auricle. With the electrodes in this position irregular beats appeared in fourteen experiments during vagal stimulation. The right vagus was stimulated in the majority of cases but those in which both vagi were used showed no noticeable qualitative differences. A beat has been considered irregular when the *As-Vs* interval was altered, when the auricular contraction was blocked. or when the type of the electrical curve was modified. Beats with *Vs-As* interval longer than the normal *As-Vs*, as well as extra ventricular systoles, have been excluded from study since the ventricular parts were not under direct electrical observation.

Of the irregularities noted under this lead 16 consisted of beats with shortened *As-Vs* intervals, four were reversed cycles with short *Vs-As* intervals, 14 were auricular contractions with conduction to the ventricle blocked and two were extra cycles with slightly lengthened *As-Vs* intervals. The curves from these 36 irregular beats showed that in all but two there was primary negativity of the sinus node. The exceptions were the two cycles with lengthened intervals. Even in these cases the seat of impulse formation may have been in some distant part and the wave of excitation for some reason have reached the auricle first. The lengthened intervals, however, render it most likely that the cycles were true extra auricular systoles, the impulses having arisen in some part of the atrium.

Sinus node and the ventricular part of the auriculo-ventricular node. In the records comparing the sinus node and the ventricular part of the auriculo-ventricular node 37 irregularities appeared during vagal stimulation. Of these 23 were beats with shortened *As-Vs* intervals, 10 were auricular beats with ventricular conduction blocked and four were examples of reversed rhythm. Of the beats with shortened *As-Vs* intervals all but two showed primary negativity in Tawara's node. Of the independent auricular beats eight arose in the sinus node and two in Tawara's node. All of the reversed

beats showed initial negativity of Tawara's node. In Fig. 1 may be seen an example of an atrio-ventricular beat just before the end of left vagal stimulation. The first cycle begins with an up stroke, indicating primary activity in the ventricular part of Tawara's node. In the second curve the down stroke is evidence that the sinus has again resumed its pacemaking function, and in accordance with this the *P-R* interval has lengthened.

Ventricular part of the auriculo-ventricular node and right auricle. With this lead 18 irregularities were observed in seven experiments. In all of these except two there was primary negativity of Tawara's node. The two exceptions were blocked auricular beats in an experiment which had normally shown precedence of the auricle over the auriculo-ventricular node.

Ventricular part of the auriculo-ventricular node and the superior vena cava. With this lead 13 irregular beats appeared, all of which were cycles with shortened *As-Vs* intervals. Without exception they showed primary negativity of Tawara's node.

Ventricular part of the auriculo-ventricular node and the coronary sulcus. It will be remembered that one electrode was placed on the coronary sulcus as near as possible to the mouth of the coronary sinus where an extension of specialised tissue from the main auriculo-ventricular mass is known to exist. In each of 13 beats showing shortened intervals, Tawara's node preceded the coronary sulcus. In five cases of blocked auricular beats Tawara's node preceded in four and in one the coronary sulcus was first.

The first of these leads, the sinus node-right auricle, was taken on the grounds that ectopic impulses during inhibition of the pacemaker by vagal stimulation might arise in the atrium. The results showed rather conclusively that only on rare occasions does the body of the auricle precede the sinus node. Even when the impulse can be shown to be arising in a distant part it reaches the sinus region before the auricular in nearly all cases. This agrees with our observations on the course of conduction in auriculo-ventricular rhythm which will be made later. The origin of ectopic impulses had to be sought then in some other part. The sinus node auriculo-ventricular lead gave immediate and positive evidence that here was a region which in a large number of irregularities preceded the sinus in action. That it should precede it in all cases was, of course, not to be expected since certain of our so-called irregularities were really nomotopic in origin. The remaining parts of the auricle had now to be compared with Tawara's node. These comparisons showed the priority of the ventricular part of the auriculo-ventricular node over the right auricle, superior vena cava and the coronary sulcus.

From the data at hand there seems to be little doubt that the majority of ectopic beats occurring during vagal stimulation of the intact heart arise in the specialised tissue of the auriculo-ventricular region. Although these findings emphasise the part played by specialised tissue in impulse formation they do not eliminate the possibility of any part of the heart functioning

as pacemaker under extraordinary circumstances. In fact, our own experiments give two examples of this very condition.

Atrio-ventricular rhythm.

A series of heart beats with the *As-Vs* intervals shortened, equal to zero or slightly negative, has come to be interpreted as an auriculo-ventricular rhythm. The reasons for this we have already discussed in our introduction. The term " nodal " rhythm we have discarded since all recent work tends to show that the normal rhythm is also a nodal rhythm ; *i.e.*, a sinus nodal rhythm. It seemed worth while to us to study electrically the sequence of events in cases of atrio-ventricular rhythm in order to localise as accurately as possible the region acting as pacemaker.

Up to the present time there have been only two criteria for determining auriculo-ventricular rhythm. The first of these has been the change in sequence of the auricular and ventricular beats. Ganter and Zahn[8] have added to this the observation that cold and heat in this condition affect the heart only when applied to some portion of the auriculo-ventricular node. The proof that the auriculo-ventricular node was acting as pacemaker has not been too well established. In the first place, the reasoning has been largely on theoretical grounds. In the second place, the accurate localisation of temperature effects necessary in the work of Zahn[23] might be questioned. The electrical methods we have employed seem to us to admit of a much more accurate application than any other yet used.

We have produced auriculo-ventricular rhythm in several ways. Theoretically vagal stimulation might be expected to accomplish this result. If a strength of stimulus could be found which would depress the normal pacemaker below the irritability of another portion of automatic tissue the latter might be expected to take up the pacemaking function. The distribution of vagal fibres would, of course, be a determining factor in securing the result. In two experiments out of 27 we have secured atrio-ventricular rhythm on stimulation of the right vagus. This is a much smaller percentage than Rothberger and Winterberg[20] secured by stimulation of the left accelerator but sufficiently large to be of interest.

Cutting around the sinus node in the heart *in situ* has also given us examples of atrio-ventricular rhythm. These cuts were made by thrusting a needle through the auricular wall into the chamber of the auricle and bringing it out again at the point desired. Along the needle the wall of the auricle was sewn down by mattress sutures. On completion of these the wall of the auricle was cut with a sharp knife directly down on the needle and the latter removed. In this way cuts in any direction or of any length could be made around the sinus node practically without hæmorrhage. Often not a single drop of blood was lost. Eight out of eleven experiments resulted in auriculo-ventricular rhythm on partial or complete excision of the sinus node. In one case, No. 20, a cut of about 2 cm. was made at the lower end of the sulcus terminalis. In two cases, Nos. 26 and 19, cuts were

made at the lower end and on the venous side of the sulcus terminalis. In two experiments, Nos. 23 and 27, the sinus node was isolated on the lower end and on both venous and auricular sides before auriculo-ventricular autonomy appeared. In experiment No. 17 the sulcus terminalis was cut across on both anterior and posterior ends, as well as isolated on the venous side. In experiment No. 24 the sinus node was isolated on all sides. In experiment No. 33 cuts were made on both venous and auricular sides. The question as to whether the connections of the sinus node at any one point are more important than others is now being studied.

In five experiments we have crushed the sinus node between the jaws of broad hæmostatic clamps. In three of these auriculo-ventricular rhythm appeared. In two cases the sulcus terminalis was pulled between the jaws of a specially devised curved clamp. The node was thus isolated by an oval of crushed tissue. In each of these cases auriculo-ventricular autonomy resulted.

In six experiments formalin has been applied to the node. The formalin was coloured with methylene blue so that a careful post-mortem examination could be made. In each case the sinus node was included in the area. In five of these experiments auriculo-ventricular rhythm appeared.

TABLE I.

	BEFORE PROCEDURE.			AFTER EFFECTS.			
Ex. No.	Cycle.	Interval		Cycle.	Interval	1st.Neg.	Remarks.
4	·306	·080	40% Formalin	·325	·000	C. Sin.	T. N. not compared.
5	·456	·096	,, ,,	·636	·000	C. Sin.	,, ,, ,,
7	·350	·100	,, ,,	·580	·060	T. N.	C. Sin. ,, ,,
9	·460	·140	,, ,,	·760	·000	T. N.	S. V. C. ,, ,,
11	·490	·070	,, ,,	·540	·000	T. N.	,, ,, ,,
12	·420	·097	Clamping	·590	·075	C. Sin.	,, ,, ,,
13	·360	·080	,,	·460	·060	C. Sin.	,, ,, ,,
3	·427	·120	Vag. Stim.	·427	·030	T. N.	All points compared.
20	·310	·132	,,	·422	·045 to ·04	T. N.	,, ,, ,,
19	·394	·150	2nd Cut	·400	·050	T. N.	,, ,, ,,
20	·340	·127	1st Cut	·439	·030	T. N.	,, ,, ,,
17	·482	·092	2nd Cut	·485	·065	C. Sin.	,, ,, ,,
23	·433	·158	3rd Cut	·454	·120	C. Sin.	,, ,, ,,
24	·380	·110	4th Cut	·484	·030	T. N.	,, ,, ,,
26	·423	·122	2nd Cut	·496	·040	T. N.	,, ,, ,,
27	·681	·100	3rd Cut	·976	·000	T. N.	,, ,, ,,
33	·341	·141	2nd Cut	·366	·127	C. Sin.	,, ,, ,,
28	·427	·140	Crushing	·541	·071	C. Sin.	Sinus node not compared.
29	·371	·138	,,	·400	·03 to ·05	C. Sin.	,, ,, ,,
32	·323	·107	,,	·466	·066	C. Sin.	,, ,, ,,

C. Sin.—Coronary Sinus.
T. N.—Ventricular part of the auriculo-ventricular node.
S. V. C.—Superior Vena Cava.

In Table I the principal data are given from the twenty successful experiments which we have performed. The length of cycles and the length

of either the *P-R* or *As-Vs* intervals are shown in their respective columns both before and after the procedure. The electrode showing primary negativity after the procedure is indicated. In the early experiments, unfortunately, not all of the electrodes were used. In the experiments involving crushing of the sinus node it was obviously impossible to make further use of the sinus electrode. In each experiment the normal sequence had been tested previously to any experimental procedure and the sinus node found to be the pacemaker.

From the data presented in this table it appears that various procedures which injure, depress or block the connection of the sinus node usually result in a condition of auriculo-ventricular rhythm. Direct injury and isolation of the node almost invariably result in this condition. These results are in agreement with those of most of the previous workers on this subject.

The appearance of auriculo-ventricular rhythm is nearly always accompanied by a lengthening of the cardiac cycle and a shortening of the *As-Vs* interval. It is always accompanied by a change in the position of the pacemaker. It may be said that there are three criteria for determining auriculo-ventricular rhythm ; lengthening of the cardiac cycle, shortening of the *As-Vs* interval and demonstrable shifting of the pacemaker to the auriculo-ventricular region. Of these the last alone is infallible. Experiment No. 3, one of our most satisfactory, shows no change in length of cycle. In experiments Nos. 12, 13 and 33 the decrease in the *As-Vs* interval is by no means striking. But in these four experiments primary negativity was in each case clearly shown to be in the auriculo-ventricular region. The method of initial negativity offers a clear demonstration that in the cases of so-called " nodal " rhythm the impulse is actually arising in the auriculo-ventricular region.

The position of our electrodes has made possible a still more accurate localisation of the seat of impulse formation. In all experiments except Nos. 4, 5 and 7 an electrode very near, if not actually on the coronary sinus, was compared with one on the ventricular part of Tawara's node. A comparison between the auricular and ventricular portions of Tawara's node was thus made possible and in certain experiments our curves show that the region around the coronary sinus was acting as pacemaker. Such was the case in eight out of seventeen experiments in which the two regions were carefully compared.

A coronary sinus rhythm, so far as we can find, was first suggested by Edens[3] as an explanation of certain arrhythmias showing a remarkably rapid rate. Erlanger and Blackmann[6] had previously called attention to the high rhythmicity of tissue in the coronary sinus region. Zahn[23] has demonstrated recently that in certain auriculo-ventricular rhythms the rate can only be influenced by changing the temperature of tissue around coronary sinus.

With the exception of experiment No. 29, the *As-Vs* intervals have been conspicuously longer in the cases of coronary sinus rhythm than in those in which the pacemaker was located in the ventricular part of the node.

There can be no fixed rule regarding this, however, judging from this same experiment. In a few beats the interval was found to be as short as ·03 sec.. These variations are probably an expression of changes in conduction and are similar to those discussed later.

Brandenburg and Hoffmann[2] first called attention to the fact that the method of sinus extirpation had a determining influence on the type of rhythm that followed. These authors believed that when the regions around the sinus were markedly stimulated during sinus extirpation the seat of impulse formation became diffuse in the body of the right auricle. It was only when the sinus was removed without excessive stimulation that an auriculo-ventricular rhythm resulted. Zahn[23] has confirmed this work with the exception that what Brandenburg and Hoffmann thought was a diffuse auricular rhythm he has shown to be really a rhythm arising in the auricular part of Tawara's node : that is, the tissue around the coronary sinus.

Our work gives some support to these conclusions of Zahn. For example, in those cases in which the sinus node was isolated by cuts at some distance from the node itself, only three times was coronary sinus rhythm produced. But in five experiments in which the node was crushed or clamped this type of rhythm resulted in each case. These results would seem to indicate that gross injury of parts around the sinus node, presumably intense mechanical stimulation, in some way raises the rhythmicity of the auricular part of the auriculo-ventricular node.

Fig. 2, 3 and 4 illustrate some of the observations previously discussed. Fig. 2 shows a comparison of sinus node and auricle at the end of a period of auriculo-ventricular rhythm induced by vagal stimulation. The auricular wave rises sharply from the slow downward stroke of the ventricular. The third beat has the normal interval. The sinus node has remained negative to the auricle throughout. Fig. 3 is a reproduction of curves from the sinus node—Tawara's node lead before and after partial isolation of the sinus node. The reversal in direction is, of course, the striking feature. That the coronary sinus may precede Tawara's node after crushing is shown in Fig. 4.

The course of the wave of excitation in auriculo-ventricular rhythm.

Our records have given us the sequence of negativity in different parts of the auricle during many cases of auriculo-ventricular rhythm. In most of these, however, the auricle had been mutilated in order to produce the condition we were studying. A determination of the path of conduction could, therefore, apply only to that particular experiment. Experiments Nos. 3 and 20, in which the rhythm was induced by vagal stimulation, are freer from such objections. The order of negativity in these hearts during auriculo-ventricular autonomy was, the ventricular part of the auriculo-ventricular node, coronary sulcus, sinus node, right auricle and superior vena cava.

An interesting thing in these observations was that the sinus became active before the right auricle. In a previous paper[7] we have shown that normally, in a large percentage of cases, Tawara's node precedes the right auricle in negativity, and we have concluded from this that conduction between the two nodes could scarcely be by way of the right auricle, as generally supposed. The sequence in auriculo-ventricular rhythm seems to agree with this hypothesis, since in reversed conduction as well, the sinus node precedes the auricle. These findings also indicate, unless the principles of reversed conduction are wholly different from normal, that the auricle receives its impulse directly from the sinus node and not by way of the auriculo-ventricular region. If the latter were the case we should expect in auriculo-ventricular rhythm that the auricle would become negative sooner, or at least as soon as the sinus region.

The effect of vagal stimulation on auriculo-ventricular rhythm.

Not only may vagal stimulation produce auriculo-ventricular rhythm but it may cause it to disappear. The latter phenomenon was first observed by Rothberger and Winterberg.[20] Stimulation of either vagus may bring about this result. Their observations were confirmed in some of our earliest experiments. The explanation of such seemingly contradictory results that vagal stimulation may either cause or abolish the rhythm probably lies in peculiarities of innervation and in the different effects that various strengths of stimuli have on the two nodes. Two points seemed of special interest in this connection ; namely, what part of the heart took up the pacemaking function after the abolition of auriculo-ventricular autonomy ; and, second, whether the change in location occurred gradually or at once.

In ten experiments we have secured data on the effects of vagal stimulation after auriculo-ventricular rhythm had been induced by cuts around the sinus node or by crushing. It should be noted that we are here referring to changes in the position of the pacemaker sufficiently permanent to result in a series of regular beats. Extrasystoles of various kinds may, of course, arise during vagal stimulation of a heart in auriculo-ventricular rhythm, although they do not seem to be so common as in the normal heart. In three of the experiments just mentioned, experiments Nos. 28, 29 and 32, the sinus node was crushed. We were unable, in these cases, to remove the pacemaker from the coronary sinus region even on many trials with various strengths of stimuli. At times there were conspicuous variations in the *As-Vs* intervals. In experiment No. 29, for example, in records during which the coronary sinus and Tawara's node were being compared with vagal stimulation the interval first increased from ·05 sec. to ·066 sec.. The following beats then decreased to ·041, ·040, and ·034. In each beat the coronary sinus retained its primary negativity. Hering[12] believes that any change of any moment in the *As-Vs* intervals speaks for a shift in the position of the pacemaker. If this be true, we had a change of location

only within the auricular part of the auriculo-ventricular node. These records also illustrated a point previously mentioned that, although usually a short interval is associated with impulse formation in the ventricular part of the node, this may not be invariably the case.

Although in the examples of coronary sinus rhythm just cited we did not succeed in getting a change in the position of the pacemaker we did succeed in experiment No. 23. Here after the fourth cut around the sinus node coronary sinus rhythm had developed. On vagus stimulation the ventricular part of the auriculo-ventricular node became negative to the coronary sinus and the *As-Vs* intervals shortened from ·105 sec. to ·02 sec.. Fig. 5 illustrates this change. After about one-half minute the coronary sinus rhythm returned. In experiment No. 17 we apparently had results similar to the preceding. After the second cut the interval was reduced from ·092 sec. to ·065 sec. and the coronary sinus was found primarily negative to all other parts of the heart. On vagal stimulation a *Vs-As* rhythm developed which gradually passed back to a positive value. Unfortunately, we did not secure a coronary sinus-Tawara's node lead, but the probabilities are that the pacemaker moved temporarily to the ventricular portion of the auriculo-ventricular node.

In experiment No. 19 no change in rhythm or character of the curves could be demonstrated on stimulation of either vagus. In experiments Nos. 20, 24, 26 and 27, all of which were examples of auriculo-ventricular rhythm with short *As-Vs* intervals and primary negativity in the ventricular portion of the node, an approximately normal interval was restored on vagal stimulation. In experiment No. 20 we did not take enough leads to locate the region which became pacemaker. The electrocardiogram, however, resumed its original shape, which was some evidence, though by no means conclusive, that the sinus node had again taken up its normal function. In experiment No. 24 the pacemaking function did not leave the auriculo-ventricular region even with the lengthening of the *As-Vs* intervals. Judging from the other experiments the pacemaker had gone to the auricular portion of the node.

In experiments Nos. 26 and 27 we secured good records from all leads and in each experiment on vagal stimulation the sinus node again took up the function of pacemaker. In Fig. 6 is shown a record from the sinus node-Tawara's node lead, in experiment No. 26 just at the beginning of right vagal stimulation. The first beat shows the short *P-R* interval which characterised the beat while the auriculo-ventricular node was leading. The initial upstroke of this curve indicates that the ventricular part of the auriculo-ventricular node was leading. In the second beat conditions are shown to have been the same except the *P-R* interval has slightly lengthened. The third beat shows an auricular wave with an initial downstroke showing that the sinus node was now first in action. In this cycle the *P-R* interval is about, ·2 sec., but it subsequently shortened somewhat. Both the right and left vagi produced similar results repeatedly. The sinus node retained

its lead throughout a two-minute period of vagal stimulation and for about one-half minute after the stimulus ceased. The auriculo-ventricular node then again became pacemaker. Experiment No. 27 gave almost identical results and for that reason need not be described in detail.

Vagal stimulation during auriculo-ventricular rhythm, consequently, may cause the pacemaker to shift from one part of the auriculo-ventricular region to another or it may abolish this rhythm altogether, allowing the sinus node again to take up the function of impulse formation. Experiments Nos. 17 and 23 illustrated the former and experiments Nos. 20, 24, 26 and 27 the latter condition.

The paramount importance of the specialised tissue in the heart is further brought out by these experiments. In our experiments no part of the heart, which did not contain such tissue, was induced to take up regular impulse formation. With the sinus node injured and the acting structures in the auriculo-ventricular region depressed by vagal inhibition, one might have expected that at times the upper parts of the auricle would become automatic. That strips of the auricles containing no specialised tissue may become rhythmical is, of course, known. It is, therefore, quite possible that even in an intact heart, under certain conditions, some part of the atrium not containing any such tissue may become the pacemaker. Our experiments, however, show that this must occur very infrequently, and that some part of the specialised tissue retains the pacemaking function even when the heart is subjected to grave experimental procedures.

The chronotropic influence of the vagi on auriculo-ventricular autonomy seems to be rather slight. We did not succeed in getting a record showing variations in rate which were not associated with a change in the location of the pacemaker. Both Rothberger and Winterberg[19] and Kuré,[14] however, have reported such observations. Their curves show only slight effects.

The changes in *As-Vs* intervals from normal to auriculo-ventricular rhythm could, of course, not be determined during many of our procedures, such as clamping and cutting around the sinus node. The changes in position of the pacemaker on vagal stimulation, however, gave us many examples of changes from one type of rhythm to the other. In most of our cases the removal of the pacemaker from the auriculo-ventricular node to the sinus was apparently more rapid than the movement from the sinus to the lower node. There were many exceptions, however, and probably no significance should be attached to the differences.

Fig. 7 shows the gradual resumption of the auriculo-ventricular type of curve after the cessation of vagal stimulation in experiment No. 26. The average *As-Vs* interval during the vagal stimulation while the sinus node was acting as pacemaker was ·093 sec.. In the second curve of the record presented this has shortened to ·077 sec.. In the third curve it is ·060 sec., and in the fourth cycle it has been reduced to ·027 at which it remained. The lead being from Tawara's node and the superior vena cava there is no change in the direction of the curves. This gradual shortening of the

intervals has been observed by Hering,[12] Kuré,[14] and Rothberger and Winterberg.[20] How is the gradual change from the sinus type to the auriculo-ventricular type of beat to be explained? As pointed out by Erlanger[5] this has been a stumbling block in our conception of auriculo-ventricular rhythm.

Two explanations have been suggested ; first, that the gradual changes in the intervals were due to a gradual shifting or wandering downward of the pacemaker ; and, second, that they were due to changes in conduction time. The former was emphasised by Hering particularly on the grounds of his physiological observation that delay in conduction time took place in Tawara's node, and the anatomical work of Aschoff who found that the auriculo-ventricular node really consisted of an auricular and a ventricular portion. This being true Hering explained variations of the *As-Vs* intervals as due to the shifting of the position of the pacemaker within the confines of the node. That this assumption is in the main correct has been demonstrated by the work of Zahn, and in a manner even freer from objection we trust by our results reported in this paper. The fact that the *As-Vs* intervals are only slightly shortened when the coronary sinus shows initial negativity and that they are greatly reduced when the ventricular portion of the node shows primary negativity seems to prove beyond question that changes in length of the *As-Vs* interval may be accounted for by changes in position of the pacemaker within the auriculo-ventricular node.

Rothberger and Winterberg[20] showed diagrammatically that in those cases in which the auriculo-ventricular rate induced by accelerator stimulation was faster than normal, it was possible for the pacemaker to jump at once to the node and the *As-Vs* interval be then gradually shortened. For a time there would be dissociation of auricles and ventricles but the systoles of the latter would keep approaching the auricular until the impulses from the node assumed dominance and the rhythm became typically auriculo-ventricular. This explanation could hardly hold in case the rhythm were slower than normal, and such is the condition in the majority of experiments in which auriculo-ventricular rhythm has been produced by depression of the sinus mechanism.

Although we believe that the gradual appearance or disappearance of auriculo-ventricular rhythm is sufficiently accounted for by the gradual shifting of the pacemaker, this does not mean that shortened *As-Vs* intervals can be obtained in no other way. Hering[12] felt that changes in conduction time could not explain variations as gross as those observed in auriculo-ventricular rhythms. We have evidences, however, that changes in conduction, heterdromie, may vary the *As-Vs* interval as well as a change in the position of the pacemaker. In experiment No. 20 we found an instance in which the sinus node resumed initial negativity before the interval had returned to normal. Fig. 8 is a reproduction of the curves. The first cycle shows an auriculo-ventricular beat. The graphic records show the *As-Vs* interval to be about ·03 sec.. The upstroke of the photographic record

indicates that the auriculo-ventricular node was primarily negative to the sinus node. The second cycle shows a P-R interval of ·05 sec. with a P wave which begins with a downstroke indicating impulse formation in the sinus. The next cycle is normal with a P-R interval of ·107 sec.. This clearly proves that the auriculo-ventricular interval may be reduced to as low a figure as ·05 sec. without the pacemaker leaving the sinus region. Whether there has been a change of position in the sinus region is an interesting question now under investigation. We have observed three examples of the phenomenon just described. Changes in conduction time cannot be disregarded therefore in studies of auriculo-ventricular autonomy even though it is not the most important factor.

The physiological fact that delay normally occurs in Tawara's node and the anatomical description of this structure suggest that the node acts much as a synapse does in the central nervous system. If in any way resistance at this point be broken down the *As-Vs* interval would be correspondingly shortened. Our curves seem to indicate that this very thing may occasionally happen. It might even be possible to have a rhythm simulating auriculo-ventricular autonomy with the sinus still acting as pacemaker.

Summary.

The origin of irregular beats during vagal stimulation, the location of the pacemaker and the course of conduction in auriculo-ventricular rhythm, and the effect of vagal stimulation on that rhythm have been studied in this paper. All the experiments were made on dog's hearts *in situ*. The method used has been that of initial negativity. Electrodes were placed on the sinus node, atrium of the right auricle, coronary sinus, superior vena cava and the auriculo-ventricular node. By means of special keys and the string galvanometer any two of these electrodes could be compared at will.

With only two exceptions all irregular beats of auricular origin during vagal stimulation were found to arise in some part of the specialised tissue, usually the auriculo-ventricular node.

Atrio-ventricular rhythm was produced by the application of formalin, by vagal stimulation, and by clamping, crushing, or cutting around the sinus node. In the majority of these cases a condition ensued characterised by a lengthened cycle and shortened *As-Vs* intervals. The only certain test of auriculo-ventricular rhythm was, however, found to be initial negativity of the auriculo-ventricular node.

Two types of auriculo-ventricular rhythm were distinguished accordingly as the impulse arose in the ventricular part of the auriculo-ventricular node or in the extension of the node around the coronary sinus. The work of Zahn has thus been confirmed by electrical methods. The *As-Vs* intervals were usually long in coronary sinus rhythms, often closely approaching the normal.

Vagal stimulation during auriculo-ventricular rhythm often caused a change in the location of the pacemaker. So long as the sinus node was not

too badly injured it could again temporarily take up the function of impulse formation. In other cases, the pacemaker moved from one part of the auriculo-ventricular node to another.

As measured by the *As-Vs* intervals the movement of the pacemaker was a gradual one. According to our experiments this gradual transition from one rhythm to another is associated with new physical locations of the pacemaker. We have, however, found a few exceptions. In one experiment during a coronary sinus rhythm the *As-Vs* interval was remarkably short. In another case the sinus node was found to be acting as pacemaker while the *As-Vs* interval was as short as ·05 sec.. Changes in the rate of conduction can, therefore, not be entirely ignored.

In no case as a result of any of the procedures to which the sinus node was subjected, did any part of the heart not containing specialised tissue act as pacemaker. In cases where the sinus node was destroyed it was found impossible to dislodge the seat of impulse formation from some part of the auriculo-ventricular node.

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Fig. 1.   Curves given by the string galvanometer with the right hand electrode on the ventricular part of Tawara's node and the left hand electrode on the sinus node.   The first beat has broken through left vagal inhibition.   The initial upstroke indicates that the beat arose in the auriculo-ventricular node.   The *P-R* interval is shortened.   In the next beat, after vagal stimulation has ceased, the downstroke shows that the sinus has again become pacemaker.

In this and all the following records the line below the shadow of the string is a mechanical one of the auricle.   Below this time is given in one-fifth sec..   An upward or downward movement in the heavy line near the time record indicates cessation or commencement of vagal stimulation.

Fig. 2.   Curves from a sinus node—auricular lead on recovery from auriculo-ventricular rhythm which was brought on by right vagal stimulation.   The first beat has a *Vs-As* interval of about ·04 sec..   The wave caused by auricular contraction rises rapidly from the slow down-stroke of the ventricular wave.   In the second part the *As- Vs* interval is about ·03 sec..   In the third beat the normal interval has returned.   Upstroke of the auricular wave shows that the sinus preceded the auricle in activity throughout.   Exp. No. 20.

Fig. 3A.   Record of a lead comparing the sinus node with the ventricular part of the auriculo-ventricular node.   Downstroke of the auricular wave shows that the sinus was acting as pacemaker.   Exp. No. 19.

Fig. 3B.   Record from same experiment as 3A, but after partial isolation of the sinus node by cuts at the lower end and venous side.   The short *P-R* interval indicates auriculo-ventricular rhythm.   Upstroke of the auricular wave is proof that the auriculo-ventricular node is first in negativity.

Fig. 4A.   Record of an auriculo-ventricular coronary sinus lead before crushing the sinus node.   Downstroke of the auricular wave shows that Tawara's node was preceding the coronary sinus.   Exp. No. 29.

Fig. 4B.   Record from the sinus experiment after crushing sinus node.   The coronary sinus now precedes the auriculo-ventricular node.

Fig. 5.   Curves from a lead comparing the ventricular part of the auriculo-ventricular node with the coronary sinus.   During vagal stimulation a coronary sinus rhythm has changed to an auriculo-ventricular.   The initial downstroke of the second beat shows that the coronary sinus again resumes the pacemaking function.   Exp. No. 23.

Fig. 6.   Curves comparing the sinus node with the auriculo-ventricular node during vagal stimulation in a case of auriculo-ventricular rhythm.   The first two beats begin with upstrokes which indicate primary negativity of the auriculo-ventricular node.   The direction of the auricular wave is reversed in the third cycle showing that the sinus node has become pacemaker.   Exp. No. 26.

Fig. 7.   Curves from an auriculo-ventricular superior vena cava lead showing the transition stages from normal to auriculo-ventricular rhythm.   The gradual increase in the *P-R* intervals is to be noted.

Fig. 8.   Curves showing the passage from an auriculo-ventricular rhythm to a normal one In the second beat the sinus node has assumed the pacemaking function before the *P-R* interval has regained its usual value.
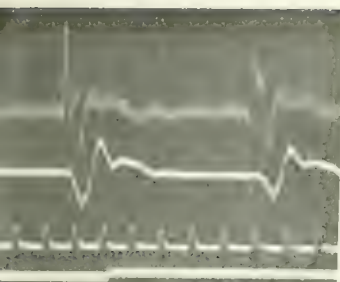
Fig 1.

Fig. 6.
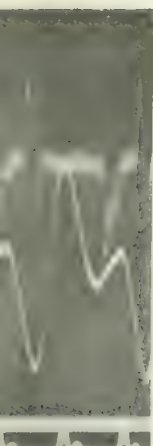
Fig. 3A.

Fig. 3B.
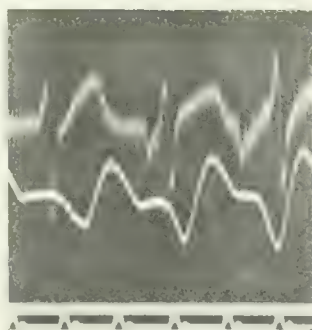
Fig 8
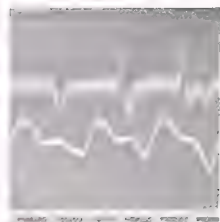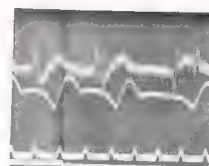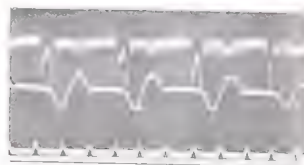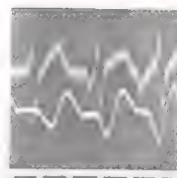
THE EFFECT OF VAGAL STIMULATION UPON ATRIO-VENTRICULAR RHYTHM.

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In describing and discussing the results of the present experiments it will be convenient to use a simple terminology, and to make certain preliminary assumptions. I shall assume it to be proved that the normal mammalian heart rhythm arises in the sino-auricular node. The rhythm will be referred to as the *S-A* rhythm, the node as the *S-A* node. I shall assume that a mechanism, consisting of contractions of auricle and ventricle which commence simultaneously or almost simultaneously (the simultaneous contractions belonging to the same heart cycle), originates in rhythmic activity of the atrio-ventricular node; and shall refer to this node as the *A-V* node and to the rhythm as the *A-V* rhythm.† The nature of the mechanism in question has not been proved finally, but a mass of evidence favours this view of its origin. Further, I shall assume it to be proved that the *A-V* node is part of a system which normally conducts impulses from auricle to ventricle and shall speak of this function as *A-V* conduction.

Rothberger and Winterberg[1] working upon the dog's heart have suggested that the cardiac nerves are distributed, to some extent at least, in a special manner, so that the right vagus and right sympathetic are said to be distributed mainly to the *S-A* node, the left vagus and left sympathetic to the *A-V* node. We are at present concerned with the vagus. These writers state that weak stimulation of the right nerve usually produces slowing of the whole heart, its action being powerful upon the *S-A* rhythm, while similar stimulation of the left nerve has a far less conspicuous action in this direction, but produces defects in *A-V* conduction. This statement has received support from a number of observers, amongst whom Cohn and myself.[1 & 2] That the *S-A* rhythm is most readily inhibited by stimulation of the right vagus is undoubted; the difference between the effects of the two nerves is profound in this respect. That *A-V* conduction is affected chiefly by stimulation of the left nerve was more open to question. At first sight the *apparent* difference is also a profound one; this is largely the result of differences in the accompanying rate of the auricular contractions; these are slower during stimulation of the right nerve; if in comparing right

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† I use this term in preference to that of "nodal rhythm" because the latter is not sufficiently distinctive, and because it has also been applied to a totally separate condition, namely, auricular fibrillation.

and left vagus the auricular rate is maintained at a constant level, the difference in effect upon A-V conduction is less conspicuous ; nevertheless it appears to exist to a slight but definite extent.[2] These facts, so it is supposed, help in supporting a hypothesis that the S-A and A-V nodes are homologous and that they are morphologically bilateral structures. But as at the outset we cannot claim that the vagus exerts its effect upon A-V conduction at the A-V node, it becomes a matter of importance to test the effect of the two nerves upon this region of the heart in another manner. We desire to know the effects of vagal stimulation upon an A-V rhythm. This method is also more desirable because we may then compare the action of the vagus upon S-A node and A-V node in respect of the same function.

Some preliminary observations have been undertaken by Rothberger and Winterberg. They assert that both right and left nerves influence impulse formation in the A-V node, stating that slowing of the new rhythm follows such stimulations. Their observations were complicated by early escape of other centres during stimulation. In one of two illustrative curves given (Fig. 10) no slowing is shown but rather a simple escape of the S-A rhythm. In the other figure (Fig. 11) slight slowing precedes similar escape. They are inclined to think from their experiments, admittedly few in number, that the left nerve has the more powerful effect. Slight slowing of a rhythm, presumably* of the same nature, was obtained in a cat by Hering in stimulating the right nerve ; and very slight slowing was observed by him in two experiments upon dogs in which the right nerve was employed. In all his experiments there was an almost immediate alteration of the intervals between auricular and ventricular systoles. At the present time we have no definite evidence of the extent of the vagal innervation of the A-V node, neither have we sufficient data to effect a comparison between those of the two sides. Data of this kind I propose to describe and review. But as previous work has indicated how varying is the distribution of the vagi to different centres, the observations have been extended. In all instances a comparison has been instituted between the action of each vagus upon each node. We shall see the effect of stimulating right and left vagus while the S-A rhythm is present and shall note that in different instances the actual or comparative effects are not the same ; we shall see effects of the same procedure upon the A-V conduction during the progress of S-A rhythm and note similar variations. In the same animals the effect upon A-V rhythm production will be described.

Method.

Dogs were employed and complete sets of records were obtained in eight instances. The animals were anaesthetised with morphia, paraldehyde and ether, and the chest opened under artificial respiration. The heart

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* I say presumably because I do not think that the rhythm in question can be identified in mechanically recorded curves with certainty. (See page 250).

being exposed and the pericardium opened a leaden tube was laid along the sulcus terminalis and connected to a reservoir of iced water. By cooling the sulcus, an *A-V* rhythm was immediately produced and could be maintained. In three of the experiments the *S-A* node was eventually destroyed by crushing and the second series of results was compared with the first ; the object of this additional procedure will be more apparent later. The vagi were exposed in the neck, and in most cases immediately cut, covered electrodes being attached and connected to a single secondary coil. The activating batteries to the primary coil were maintained at a constant voltage throughout all experiments. The records were taken electrocardio-graphically from the right fore-limb and left hind-limb. Simultaneous myocardiograms were taken from the right auricular appendix and across the ventricle from right to left margin.

A series of records was taken showing the effects of right and left vagal stimulation upon the *S-A* rhythm and the *A-V* rhythm ; the secondary coil being maintained as a rule at a fixed distance. Shorter stimulation and longer stimulation were employed, and from time to time the strength of the stimulation current was suitably varied. In any series the records were taken in quick succession so that the conditions might be kept as uniform as possible.

The rhythm investigated ; remarks upon the records and intervals.

When cold is applied to the sulcus terminalis, the *S-A* rhythm slows and, as Ganter and Zahn and others have shown, the mechanism of the heart frequently alters. The retardation of the rhythm of the natural pacemaker permits the escape of other centres. Using low temperatures I have always obtained escape of this kind, but the mechanism which becomes established is not of constant type.

Two distinct types of heart action are seen.

1. *A-V rhythm.* In this, which is the commonest, the contraction of auricle and ventricle is practically simultaneous, though in the electro-cardiographic curves the auricle almost always slightly precedes the ventricle. A characteristic example of the change from one mechanism to the other is seen in Fig. 1. The cold was applied at the point marked by the signal. Slowing is seen in the next cycles ; then the *P-R* interval drops to ·049* seconds in the sixth cycle of the figure, though both the *P* summit and ventricular complex retain the normal outline : it is at this, the fifth cycle, that the *A-V* impulse has first escaped, but the auricle being already in contraction from an *S-A* impulse, does not respond to it. The next and last three cycles of the curve show the established *A-V* rhythm. The form of the electrocardiogram is very characteristic ; the ventricular complex is of

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* Where figures are given to three decimal points, the measurements have been made upon a comparator and the error is in no case greater than ·005 seconds ; usually it is much less.

normal outline, the usual P summit has vanished and is replaced by a small dip immediately before R and resembling a diminutive Q deflection. This little depression which, as I have abundant evidence to show, signals the onset of auricular contraction, is seen in most of those curves of mine which belong to this group. The As-Vs interval which can be measured accurately only in the electrocardiogram is ·027 seconds. In the tables attached to this paper the measurement of the As-Vs interval (usually P-R) is given for the normal and ectopic rhythm in each experiment; this is very necessary for the magnitude of the interval is one of our best guides to the point of origin of a new rhythm.

There is another feature of the change which is very constant, and is seen in a comparison of the As-Vs interval, measured in the mechanical curves and electrocardiograms. While the normal rhythm is in progress the mechanically recorded As-Vs interval is less than the P-R interval by an average of ·017 seconds. *This discrepancy is increased by an additional ·009 seconds when the A-V rhythm becomes established.* The discrepancies are due to differences in the transmission intervals from the starting points of contraction to the levers. The added discrepancy in the case of the A-V rhythm expresses the difference between two transmission intervals, namely, the S-A node to auricular lever and the A-V node to auricular lever; the latter is always the greater when the auricular curve is taken from the right appendix. The auricular curve of Fig. 1 was from the right appendix, as in all the present figures. As-Vs intervals, measured in mechanical curves, are never strictly accurate indices of the commencing contraction wave, and under certain circumstances the error may be very material. It may be so great that while the auricle enters contraction actually before the ventricle, the reverse is shown. I emphasise these intervals, not only to point out this source of error but also because the mechanical curves in combination with the electrocardiograms give a clue to the distance of the new auricular centre from the auricular lever.

2. On occasion a mechanism of a different kind is observed. It is illustrated by Fig. 2. Slowing as a result of cold applied commences after the third auricular beat. The shape of the auricular summit alters at its sixth appearance. The first alteration we may leave for the moment. The remaining P summits are inverted. The As-Vs intervals before the change shows, as it happens, only a slight discrepancy; after the change the discrepancy amounts to ·02 seconds or more. Where does this new rhythm arise? I suggest that its point of origin is also to be sought near the auriculo-ventricular ring, and for these reasons: (a) P is inverted as it is when the rhythm arises in the A-V node itself; (b) the distance between it and the appendicular lever is considerably greater than the distance between the S-A node and lever (as in Fig. 1). The actual excess expressed in time is ·02 seconds. In Fig. 1 it was ·009 seconds. In the present instance a much larger animal was utilised, sufficiently accounting for the difference; (c)

the P-R interval is slightly reduced, approximately by ·015 seconds; showing that the centre is nearer to the ventricle than the S-A node by this transmission time. Whatever its actual origin it must be clearly distinguished from the first mechanism discussed, for the reduction of the P-R interval is but slight. Fig. 3 shows the A-V rhythm in the same animal during a separate observation. Comparing the two figures, it is seen that in each mechanism P comes with a downstroke; but in Fig. 3 the P-R interval is only ·023 seconds.

I describe the second type of mechanism chiefly that I may be understood in stating that the observations upon vagal inhibition hereafter recorded apply in the main to the A-V rhythm confining the term to mechanisms in which the P-R interval is less than ·04–·05 seconds; a few observations have also been made upon similar rhythms in which the intervals were longer, but the opportunity does not often present itself.

But before leaving this particular curve (Fig. 2), I may draw attention to the curious change in the shape of the P summits at the transition. The centre P summit is a combination of the normal and invert P summit, and has been produced in all probability by two excitation waves, one started above, the other below, and meeting in the walls of the auricle. I accept this explanation in opposition to a view of a third centre of impulse formation because (a) the P summit in question is of transitional form; (b) it is found that both normal and invert P are to be anticipated at this point to continue the preceding and succeeding rhythm*; (c) because these transitions are very frequently encountered in these experiments (the last upright P of Fig. 3 is transitional, it is reduced in size) and *only where the clashing of the two excitation waves is expected*; and (d) transitional forms between the S-A and A-V types are seen when the P-R interval is reduced to ·050 seconds or less; the less the reduction the more nearly is P of the S-A type, the greater the reduction the more nearly is P of the A-V type.

I give a clinical instance of a parallel phenomenon in Fig. 5. Here the transition is more gradual and therefore more striking.

Vagal stimulation.

The observations from which my conclusions are drawn are fully exemplified in the tables accompanying this article; as I shall often refer to these tables, the manner of tabulating is first described.

Description of tables. In the third column I give the nature of the rhythm, normal, A-V (or simply ectopic rhythm, where the actual point of origin seems more open to question) and immediately afterwards, in brackets, the length of the As-Vs interval. If the interval was measured in the electrocardiogram it is indicated. These time intervals are given in

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* The shortened interval of ·067 seconds is in this instance the result of a primarily isoelectric state, when the upstroke of the normal P and the downstroke of the invert P first combine.

seconds and to three places of decimals ; the measurements were made with a comparator, and the error is in no case greater than ·005 seconds. All the remaining intervals of the tables are given in twenty-fifths of a second and to the nearest fiftieth of a second. To complete the third column the lengths before stimulation of several cycles of the rhythm tested are given ; these intervals apply to auricle and ventricle indifferently. In the fourth column I give the nerve stimulated and the length of stimulation. In the fifth column the distance of the secondary coil during stimulation. The effects are stated in detail in the sixth column, in two lines ; the top one gives the interauricular, the bottom one the interventricular distance, from cycle to cycle, and measured in the electrocardiograms in practically all cases. In the auricular line, heavy type indicates that the pause precedes an auricular contraction arising in the S-A node, as indicated by the electrocardiogram ; light type indicates a pause preceding an auricular beat of different origin ; if unmarked it may be taken as of A-V nodal origin ; if marked with an asterisk its site of origin is discussed in the remark column. Heavy type in the ventricular column indicates a pause preceding an escape from a ventricular focus ; light type indicates that it precedes a ventricular beat which is a response to the auricle or A-V node.

Thus in Table I (obs. 1), the rhythm is normal, the P-R interval being ·095 seconds and the original lengths of cycles $\frac{13 \cdot 5}{25}$ sec. &c. ; the right vagus was stimulated with the coil at 22 cm. for two seconds. The effect of stimulation is simple slowing of the whole heart, the auricular beats coming constantly from the S-A node (heavy type), the ventricular beats following them (light type) ; the absence of appreciable change in the P-R interval is indicated by the identity of the intervals in the two columns. The effect of right vagal stimulation upon A-V rhythm is seen in the third observation of this table ; the A-V rhythm is unchanged for the first cycle (light type and similar intervals, 24·0, above and below) ; the next cycle, $\frac{44 \cdot 0}{38 \cdot 0}$, ends in an escape of the S-A node and of the ventricle simultaneously. The fourth observation is similar but here the S-A node escapes at once (**33·0**), the ventricle following upon it ; the interval of the latter is consequently 34·5. Again in the second observation, the commencement of the fourth cycle is marked by slight prolongation of the P-R interval which is righted a few cycles later ; this is indicated in the intervals of the third, fifth and sixth cycles. The method of tabulating should be clear if illustrative figures are compared with the corresponding observations (see figures).

Effect of vagi on " S-A " rhythm.

In the eight experiments recorded, the effect of the right vagus upon the S-A rhythm has been more profound than the left vagus on seven occasions ; in one experiment (Table I) the effects were about equal. So far as apparent heart-block is concerned, the right produced a greater effect

than the left vagus on one occasion only (Table V); the left had the greater effect in five instances, and in the remaining two there was little to choose between them. These observations are purely confirmatory of past observations.

Effects during " A-V " rhythm.

The effects of vagal stimulation upon the heart responding to an *A-V* rhythm vary very greatly. Not only do they vary according to the comparative control exerted by one or other vagus; but the results are complicated by the condition of the other centres of impulse formation. I may conveniently describe the results under separate headings :—

1. *Escape of the S-A node ; comparison of vagal effects upon S-A and A-V node.* If the rhythm of the *S-A* node is reduced by cooling, and an *A-V* rhythm becomes established as a consequence, and if one or other vagus is then stimulated, the heart shows almost immediate slowing. In not a few experiments the first or second cycle of the slow action is terminated by a *P* summit of natural form, indicating a return of the *S-A* rhythm.[1] Once there has been escape of this kind (Fig. 6) it is maintained during the progress of stimulation and for some little while afterwards ; eventually, as the observation is continued and the cold maintained, an *A-V* rhythm is always re-established. It goes without saying that the escape is the result, not of the stimulation, but of the slowing of the *A-V* rhythm consequent upon stimulation. When the escape of the *S-A* node occurs early during the observation, the intervals do not express the full effects of vagus upon the *A-V* node. We know that the *A-V* rhythm has been retarded to this extent at least (Fig. 6) but we do not know the actual extent of the retardation. The intervals actually represent the effect of vagal stimulation upon the cooled *S-A* node, and this effect is always more profound, in the absolute sense, than upon the uncooled *S-A* node (see Table VIII, obs. 1 and 2). Escape of the *S-A* node occurs in the great majority of observations in which the left nerve is stimulated, and also in most instances when the right nerve is stimulated. Such observations (see Tables I and II, and the first part of Table IV) show that, absolutely, the effect of the vagus upon the *A-V* node is greater than upon the *S-A* node. This statement applies to both nerves ; it applies with equal force, as might be expected, to the left nerve, for the influence of this nerve upon the *S-A* node is relatively small. It should not be forgotten that the comparison is not between the normal rhythmicity of the two nodes ; it is between the rhythmicity of the cooled *S-A* node and the normal rhythmicity of the *A-V* node. Even under these circumstances, where the effect of the vagi upon the *S-A* node is enhanced by applying cold, the *absolute* effect is greater upon the *A-V* node.* I have spoken of the absolute effect, meaning the

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* A solitary exception will be noted later.

actual rate obtained by stimulation. *Relatively* it is also greater in the experiments to which I refer, for the *S-A* node is cooled and its rate is therefore initially less than that of the *A-V* node (whence the original establishment of the *A-V* rhythm). The vagi are acting upon two centres of impulse formation. If we judge the dynamic condition of these centres purely by the rate at which they form their impulses, we must then conclude that *relatively and absolutely the effect of the vagi is greater upon the A-V node than upon the S-A node in the majority of animals in which the effects can be compared.* It is customary to regard the *A-V* node as a relatively hypodynamic centre ; its hypodynamicity is physiological. A comparison with hypodynamicity produced by cold is perhaps questionable. But allowing such a comparison to be a fair one, then our conclusion holds good. It is perhaps less remarkable than might appear at first, for as the *A-V* node has a relatively high grade of rhythmicity in the dog's heart, an escape of its rhythm would be a common event during slight inhibition were it not that it is powerfully controlled. It may be that in this control we have a provision against synchronous action of the two chambers in the dog's heart. The rate of the dog's heart is subject under natural circumstances to very considerable fluctuations ; were the *A-V* node free, synchronous action of auricle and ventricle would be a common event.

2. *Comparison of right and left vagus upon A-V node.* When there is no escape of the *S-A* node until in the late phases of stimulation a comparison may be instituted between the relative effects of right and left vagus upon the *A-V* node. Thus in the experiment of Table III, observations 2 and 8 may be compared (Fig. 7 and 8) and also observations 10 and 12. The first few cycles in each curve are controlled by the *A-V* node ; the right nerve produced more rapid and profound slowing. When too, as sometimes happens, the slowing produced by stimulation of the left nerve is insufficient to lead to escape of the *S-A* node, the degree of slowing may be compared with the greater slowing of the heart as it is given by the right vagus, whether the *S-A* node escapes or not. Thus in the experiment of Table IV, stimulation of the right vagus with a weak current produces (obs. 2) profound slowing of the heart with immediate escape of the *S-A* node ; we may assume that the slowing of the *A-V* rhythm is more profound than the apparent slowing in this observation. Stronger stimulation of the left nerve (obs. 5) leads on the other hand to slight slowing of the *A-V* rhythm without escape until the fourth cycle.

Judged by such comparisons, and they are possible in four experiments (Tables III, IV, VI and VII) the right vagus acted more powerfully upon the *A-V* node in all but one instance (Table VII). Here the left vagus predominated (later, this experiment is more fully described).

In two animals of the same series (Tables III and IV) a comparison was also instituted after destroying the *S-A* node by clamping, so as to prevent escape ; preponderance of the right vagus was still observed in both (Fig. 9 and 10) ; and the same result was obtained in another experiment (Table V).

Thus in five experiments in which the effects of right and left vagal stimulation upon the A-V rhythm could be compared, the right nerve was regularly the more effective in four; in the fifth, as I have stated, reverse relations were observed.

In these clamp experiments a large area of the tissue of the right auricle was destroyed, including a band about $1\frac{1}{2}$ to 2 cm. broad and running the whole length of the sulcus terminalis. The area destroyed included in fact the whole of the tissue previously cooled.

2. *An exceptional experiment.* In a single dog a very remarkable effect was observed. We have seen that in most animals both vagi have a more powerful effect upon the A-V node than upon the S-A node. This direct observation accords with a common experience, namely, that escape of the A-V node during stimulation of the vagi is rare. We have also seen that as a rule the right vagus exerts a more profound influence upon the A-V node than does the left nerve. In the exceptional case which I now describe the vagal control was different. In this animal the right vagus controlled the S-A node to a greater extent than the A-V node; and the left nerve controlled the A-V node to a greater extent than the right nerve; in other respects the usual rules were followed, for the right nerve controlled the S-A node to a greater extent than the left nerve and the left nerve had a more profound effect upon the A-V node than upon the S-A node. The usual and exceptional effects may be grasped perhaps more readily if they are expressed in tabular form.

Usual relations.

S-A node Effect of	A-V node Effect of	Right vagus Effect on	Left vagus Effect on
R.V. + L.V.—	R.V. + L.V.—	S A N — A V N +	S A N — A V N +

Exceptional relations.

R.V. + L.V.—	R.V. — L.V. +	S A N + A V N —	S A N — A V N +

The effect of this curiously distributed control is seen in Table VII. It is summed up in the following statements :—

(A) During the S-A rhythm the right vagus produced slowing of the S-A rhythm and almost immediate escape of the A-V node (Fig. 11); the S-A rhythm subsequently re-appearing where stimulation was short but showing considerable retardation.*

(B) During the S-A rhythm the left vagus produced a lesser grade of slowing; it was simple slowing and the A-V rhythm was maintained in abeyance.

(C) During A-V rhythm, the right vagus produced a very slight and simple slowing (less than that produced during the S-A rhythm) and the S-A rhythm was held in abeyance.

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* Thus, although the effect on the S-A node was less profound than upon the A-V node, the former seemed to be more lasting.

(D) During the *A-V* rhythm, the left vagus produced slowing (to a greater extent than stimulation of the right nerve), usually accompanied by escape of the cooled *S-A* rhythm. (Fig. 12.)*

Alteration of the " As-Vs " interval.

Stimulation of the vagus during the progress of the normal rhythm produces heart-block. This heart-block may be manifested in two ways ; either there are dropped beats, the ventricle failing to respond to the auricle, or there is a prolongation of the interval *P-R*. The last event is almost constant upon stimulating the left nerve and is not infrequent upon stimulation of the right. In the eight experiments, heart-block of this kind was seen in seven, and on several occasions preceded to the higher grades of block, namely dropped beats. I wish to emphasise the frequence of conspicuous heart-block in the experiments described in this paper.

When true *A-V* rhythm, that is to say, a mechanism in which the *P-R* interval is less than ·04 seconds, has become established and the vagi are stimulated, an alteration of the intervals has been invariable, with the solitary exception of an experiment (Table I) in which early escape prevented its appearance. *But the change is in the opposite direction and consists of a reduction of the " P-R " interval from its original value to 0·00 seconds or to a minus quantity.* This reduction is usually slight ; on occasion it may be considerable. I have seen precisely similar changes in the cat upon stimulating the vagus while *A-V* rhythm was present. It occurs with both nerves. It is in striking contrast to the usual phenomenon while the normal rhythm prevails, namely an increase of interval. It cannot be attributed to a simultaneous change in the level at which the impulse arises. The change and the recovery from it is as a rule very gradual, being spread over a number of cycles ; where it can be identified the auricular complex maintains its form ; and there are no accompanying irregularities of auricle or ventricle, but simply slowing of each ; at the end of stimulation there is gradual lengthening of the interval as the heart quickens and a return to, or beyond, the former values. I may illustrate the change by giving the successive intervals as measured with the comparator in two curves. The first series is taken from Fig. 12 ; starting one cycle before the commencement of the figure the intervals are given up to the cycle before the escape of the *S-A* node. The second series is from the sixth observation of the experiment given in Table VII.

1. (Table VII, obs. 8). Successive *As-Vs* interval in seconds (maximal error ·002 seconds) +·0119, +·0087, +·0088 (left vagus stimulated, coil 16 cm.) +·0039, +·0011, —·0056, —·0073, —·0173, —·0246,—·0279, —·0284, —·0332, —·0347 (escape of auricle, stimulation continuing).

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* The actual intervals in this table should receive close examination, the rates being compared in the several observations ; they are peculiarly instructive.

2. (Table VII, obs. 6). Successive *P-R* intervals (maximal error
·001 seconds) ·0317, ·0305, ·0317 (left vagus stimulated, coil at 19 cm.),
·0312, ·0307, ·0317, ·0292, ·0298, ·0299, ·0286, ·0280, ·0239 (cessation of
stimulation), ·0225, ·0230, ·0232, ·0268, ·0292, ·0306, ·0330, ·0363, ·0378,
·0402.

The change is so slight from beat to beat that tables, arranged in the manner
of those at the end of this article, will not always show it ; but it is perfectly
clear in many of the accompanying figures, and notably in Fig. 8, 11 and 12.
A change in focus yields a sudden alteration of interval and usually a
shortening of the corresponding cycle. This last phenomenon has been
witnessed on several occasions during the course of my experiments ; it is a
distinct condition and is exemplified by Table IV and VI. Thus in Table IV
(obs. 5), the change is abrupt and the beats which follow are relatively rapid.
The same statement applies to Table VI (obs. 9 and 11). Moreover, when
there is escape of this kind, it occurs also when the *S-A* rhythm is distributed
by vagal stimulation (see tables).

To what then is the reduction of interval, so constant in proper *A-V*
rhythm, due* ? It should be evident that theoretically two forms of heart-
block may occur in *A-V* rhythm : if the block were between node and
ventricle it would be of the usual type. There would be, as is actually found
to be the case,† a prolongation of the *P-R* interval and eventually dropped
ventricular contractions. On the other hand, if a block occurs between node
and auricle, then a reverse change should be seen, namely a reduction of the
P-R interval. Such is evidently the nature of the disturbance which we
are considering. It is proved by Fig. 12a, in which the reduction proceeds
and until the *As-Vs* becomes a minus quantity and, increasing, the auricle
fails to respond.‡ This " reversed " heart-block is of much interest ; for as we
shall see it gives a definite clue to the level at which the vagus acts in producing
heart-block. We may conveniently postpone a consideration of this question
until the remaining experiments have been considered.

*The action of the vagi upon the rhythms in which the " As-Vs " interval
is greater.*

During the course of these experiments the effects of the vagi have
been observed upon rhythms in which the *As-Vs* interval has exceeded
·05 seconds ; it seems desirable to give these results separately. The
observations are less complete for the reason that such rhythms are difficult
to obtain and maintain with constancy. I have tabulated two series of these

* In the whole series a solitary and insignificant exception has been seen (Table V, obs. 17).
In this there was slight prolongation of the interval ; the measurements ·0211, ·0191 (left vagus
stimulated), ·0242, ·0220, ·0274, ·0340, ·0358, ·0345, ·0327 (max. error ·002 sec.).

† Such heart-block, produced by applying a clamp to the *A-V* bundle is described by
Meakins on page 281 of this *Journal*

‡ The measurements of this figure were made with the comparator and are expressed in seconds,
as opposed to those of the remaining figures. The *As-As, As-Vs* and *Vs-Vs* intervals are given.

and may discuss them briefly. The first series is to be found in the first part of Table V. In the new rhythm the P-R interval was but slightly reduced (normal ·092, ectopic ·089 sec.) and P instead of being of the tall and positive form showed two phases, the first decidedly negative, the second a small positive effect. The point of origin of such a rhythm is not definitely known but as I have suggested in an earlier part of this paper, probably comes from the region of the A-V ring.

Comparing the effects of the right vagus upon the S-A rhythm and new rhythm in this animal : the influence of this nerve upon the S-A rhythm was always relatively and sometimes absolutely more profound. High grades of partial heart-block were produced between auricle and ventricle in both circumstances.

Comparing the effects of the left vagus : the influence of this nerve upon the new rhythm was greater relatively and absolutely than upon the S-A rhythm. Thus in obs. 4 and 5, the effect upon the normal rhythm is slight, upon the new rhythm considerable. In obs. 10 and 11, the difference is also conspicuous. Partial heart-block was also seen during stimulation of the left vagus in this experiment, and on all occasions.

Comparing the effects of the two vagi : the right nerve influenced the S-A rhythm more than the left ; on one occasion (obs. 5 and 7) the same nerve had the greater influence upon the new centre, on another occasion (obs. 9 and 11) the left nerve had rather more effect than the right.

In the second series (Table VIII) a new rhythm of similar character was under observation. The P summit was of the same form ; the reduction of the P-R interval was rather greater, being from the normal of ·132 seconds to ·074 seconds.

Comparing the effects of vagal stimulation upon S-A rhythm and new rhythm : the influence of both nerves was greater upon the new rhythm, as evidenced by the greater degree of slowing and also by the frequent and early escape of the S-A node during stimulation in obs. 3, 5, 7, &c.. These effects are in contrast to those found in the first experiment (Table V).* The effects of the two vagi could not be compared on account of invariable escape from other centres.

Vagal heart-block.

We may return to a further consideration of heart-block as it is produced by vagal stimulation. We have seen that when true A-V rhythm is present, the usual or forward heart-block which interrupts a normally sequential heart is replaced by what I term " reversed " block. It is to be remarked

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* An interesting occurrence, but one for which no explanation seems to be forthcoming, is charted in obs. 10 to 13. Towards the end of the experiment, while the S-A rhythm was established, the left vagus gave with great regularity short runs of rapid beats of ventricular origin (Fig. 13). No sign of such beats could be obtained when the same vagus was stimulated after the establishment of the new rhythm although the positive and negative observations were repeated many times alternately.

that prolongation or reduction of the interval in a given animal is clearly connected with the previous origin of the rhythm. If, too, the starting point of the rhythm changes from S-A node to A-V node (or *vice versa*) during the course of stimulation a widening interval is replaced by a reducing interval (or *vice versa*). We have also, by way of contrast, an experiment in which, though the auricular and ventricular contractions were to some extent simultaneous (Table V), the P-R interval being ·089 seconds, forward heart-block was conspicuous. In an early part of this paper I have discussed the probable origin of such rhythms, regarding them as emanating from the lowermost levels of the auricle, the uppermost levels of the junctional tissue. This view harmonises with that previously expressed by Hering.[3] The contrast in the action of the vagus upon two rhythms which are clearly such close neighbours is remarkable. Nevertheless it is susceptible to explanation if we conclude, as I think we must now conclude, that the vagus acts, in producing heart-block, upon the A-V node or its immediate vicinity. We know that it cannot exert its influence solely upon the A-V bundle, for if so, during A-V rhythm, a forward heart-block would be produced (see Meakins' evidence). There is another reason for imagining that it is the node which the vagus depresses. Although the auricle may fail to respond on occasion, such as that cited, to A-V impulses, yet this phenomenon is rare : the degree of reversed heart-block is almost always slight and on a solitary occasion (obs. 17, Table VII) a very slight grade of forward block was witnessed. This in itself calls for attention ; the degree of block witnessed is not the degree anticipated from observations upon the S-A rhythm in the same animal. If the vagus acts in producing heart-block, as might be supposed, mainly and uniformly upon Tawara's node, and the rhythm affected arises at a low level in this node, then the influence could be twofold. The vagus would tend to produce forward heart-block in virtue of its action upon the shorter and lower reaches of the tissue, and reversed heart-block in greater degree in virtue of its action upon the longer and upper reaches of the structure. The two effects would tend to counteract each other, though reversed heart-block would predominate.

As an alternative explanation, it might be suggested that the predominant action of the vagus is at the precise level at which the rhythm originates, but that it also acts upon the auriculo-ventricular junction above the node, and upon the bundle below it, the former action being somewhat the greater. This explanation would equally meet the case.

Whichever view may be adopted we are left with the main conclusion, that the chief action of the vagus is at the node or in its immediate neighbourhood. And this conclusion applies not only to a heart exhibiting A-V rhythm but to S-A rhythm as well. The experiment given in Table VI should be attentively studied. While the A-V rhythm is present and the heart comes under the influence of the vagus, reversed heart-block is noted ; immediately at the escape of the new centre from a higher level, the relations are altered and forward heart-block is found.

Summary.

1. If after A-V rhythm is established by cooling the S-A node, the vagus is stimulated, the usual effect is slowing with escape of the cooled S-A node. This statement applies to both nerves, but especially to the left.

2. This fact, and a comparison of the actual degree of slowing produced by vagus stimulation upon S-A and A-V rhythm, leads to the conclusion that the influence of both vagi is usually more profound, relatively and absolutely, upon the A-V rhythm than upon the S-A rhythm. It is to this that the infrequent escape of the S-A node, during vagal stimulation, is due.

3. Although it may be true that the right vagus has more influence than the left in producing A-V heart-block in the dog, yet the right nerve usually appears to have a larger control than the left upon A-V rhythm.

4. The relative control of the vagi over the A-V rhythm is not constant from animal to animal. While in most the right nerve predominates, yet the reverse may be true. In an exceptional animal the control in order of magnitude was as follows :

1 and *2* $\begin{cases} \text{Right vagus upon } S\text{-}A \text{ rhythm} \\ \text{Left vagus upon } A\text{-}V \text{ rhythm.} \end{cases}$

3 and *4* $\begin{cases} \text{Left vagus upon } S\text{-}A \text{ rhythm.} \\ \text{Right vagus upon } A\text{-}V \text{ rhythm.} \end{cases}$

The usual order is :—

1   Right vagus upon A-V rhythm.

2 and *3* $\begin{cases} \text{Right vagus upon } S\text{-}A \text{ rhythm.} \\ \text{Left vagus upon } A\text{-}V \text{ rhythm.} \end{cases}$

4   Left vagus upon S-A rhythm.

5. When the auricle or ventricle beat partly or wholly together, the quality of the heart-block which results from vagal stimulation varies according to the length of the As-Vs interval.

6. The almost constant absence of the usual form of heart-block when the vagus is stimulated and proper A-V rhythm is present, and the presence of reversed block, shows that the vagus in producing heart-block, acts, predominantly at least, on the auricular side of the tissue originating A-V rhythm ; at the same time it acts chiefly on the node itself.

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Fig. 11.

Fig. 12.

Fig. 10.

Fig. 11.

Fig. 12.

Fig. 13.
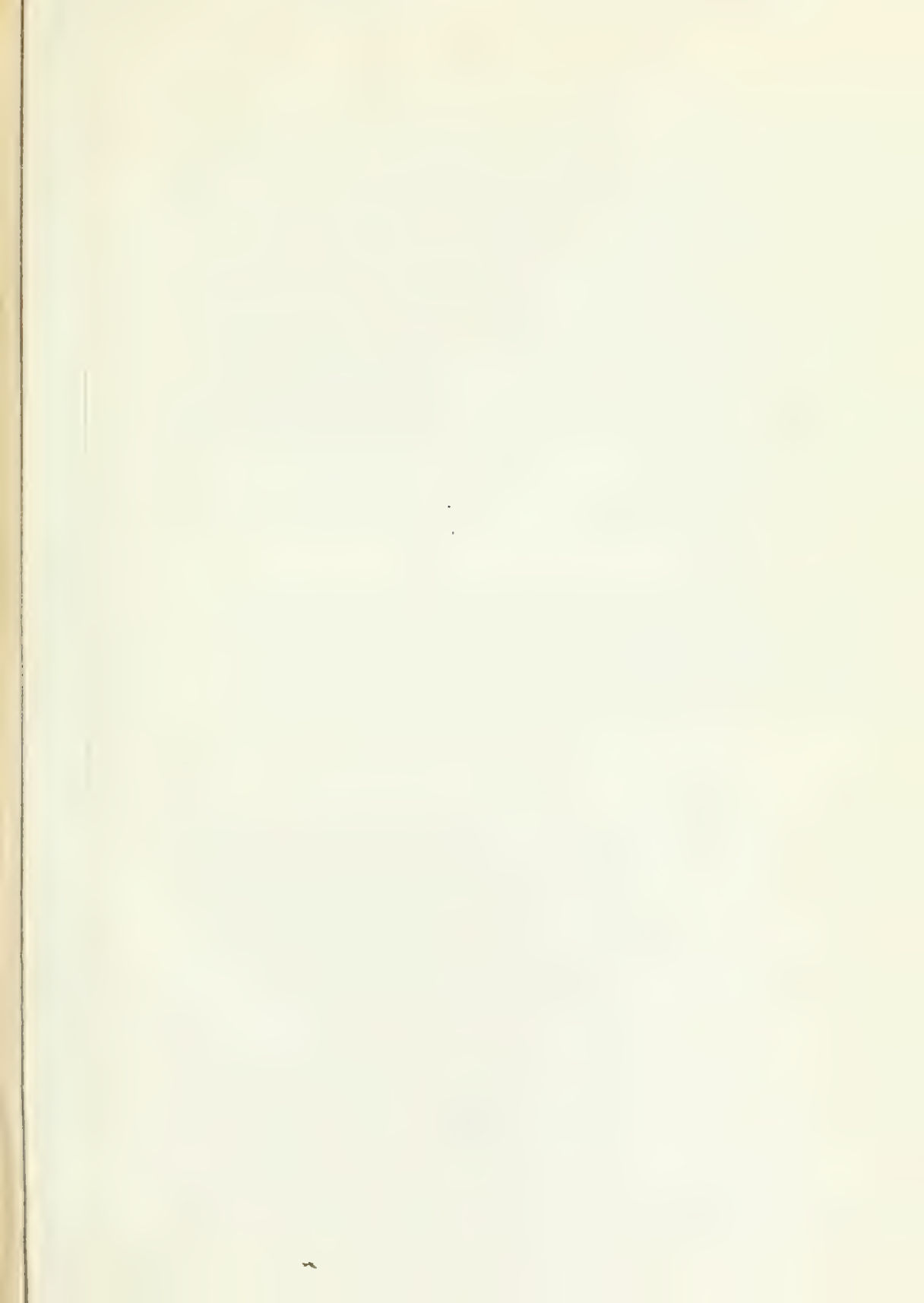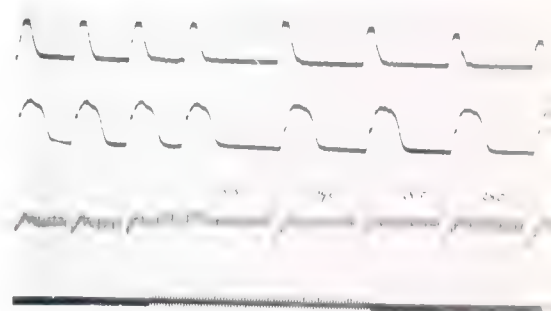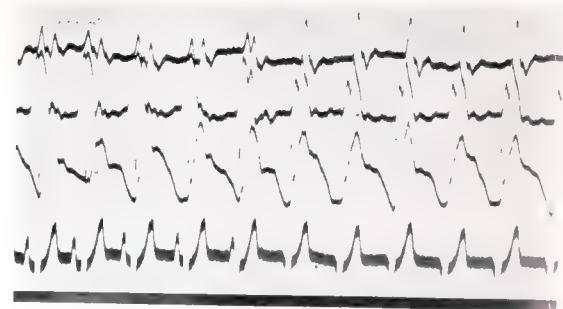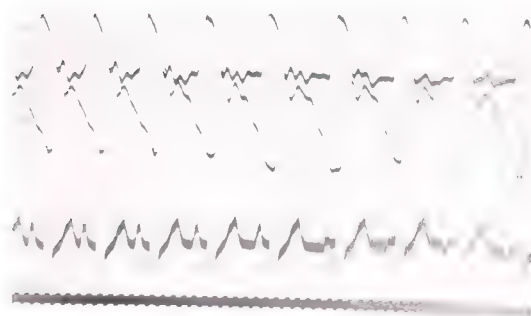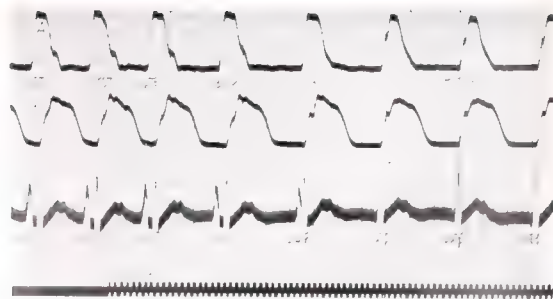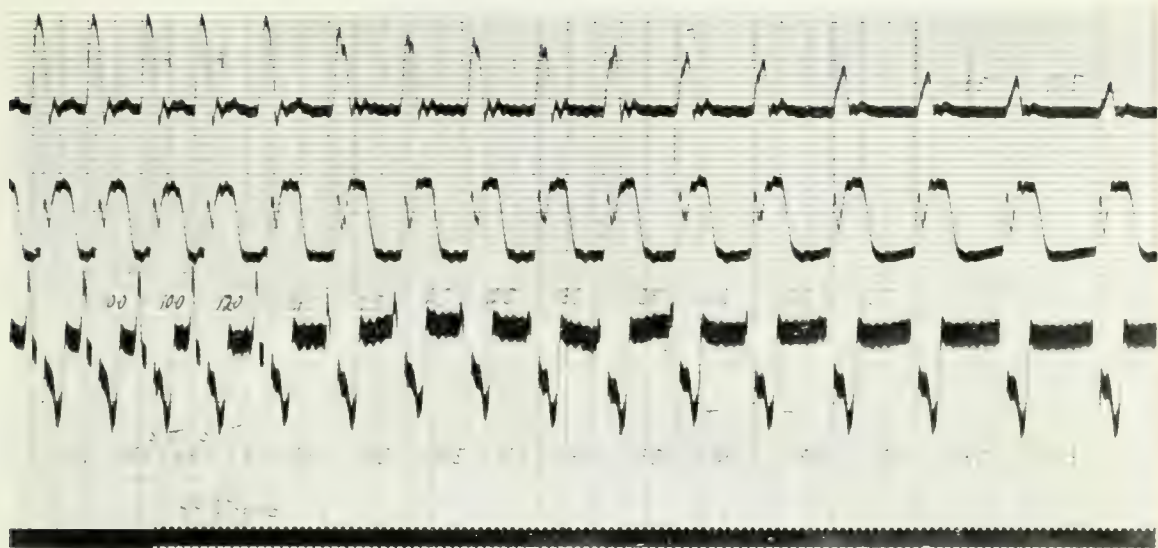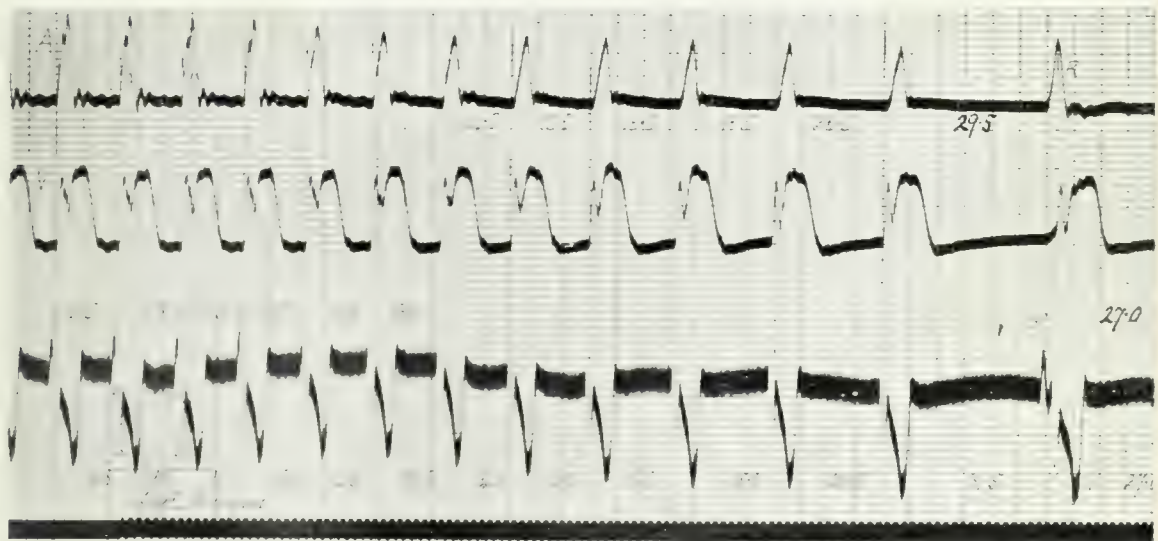
TABLE I. (DOG EE).

Obs.	Rhythm and rate before stimulation.	Nerve and length of stimulation.	Coil at cm.	EFFECT.	REMARKS.
Right 1	*Vagus cut.* Normal (*P-R* = ·095 sec.) 13·5, 13·5	R.V. 50*	20½	*As.* **14·5***,**15·5**, **16·0**, **17·0**, **16·0**, **15·5**, **15·0**, **14·5** *Vs.* 14·5, 15·5, 16·0, 17·0, 16·0, 15·5, 15·0, 14·5	Simple slowing.
2	Normal, 14·5, 14·0	R.V. 95	18½	*As.* **15·0**, **18·0**, **20·0**, **21·5**, **22·5**, **21·0**, **20·0**, **20·0** *Vs.* 15·0, 18·0, 21·0, 21·5, 22·0, 20·5, 20·0, 20·0 *Vs.* **20·0**, **20·0**, **19·0**, **18·0** *Vs.* 20·0, 20·0, 19·0, 18·0	Slowing and prolonged *P-R.*
3	*A-V* node (*P-R* = ·026 sec.) 17·0, 17·0, 17·5	R.V. 87	18½	*As.* 24·0,　　　**44·0**, **34·0**, **32·5**, **27·0**, **26·0**, **25·0**, **19·0** *Vs.* 24·0, **38·0**, 10·0, 33·0, 32·5, 27·0, 26·0, 25·0, 19·0	Slowing ; escape of ventricle and auricle ; prolonged *P-R.*
4	*A-V* node, 20·0, 20·0	R.V. 100	17½	*As.* **33·0**, **34·0**, **36·0**, **31·0**, **29·5**, **29·0**, **28·5**, **28·0**, **28·0** *Vs.* 34·5, 34·0, 35·5, 31·0, 29·5, 29·0, 28·5, 28·0, 28·0	Slowing with escape of auricle.
5	Normal, 16·0, 16·0	R.V. 95	17½	*As.* **19·0**, **20·0**, **21·5**, **22·0**, **22·5**, **21·0**, **20·0**, **20·0**, *Vs.* 19·0, 21·0, 22·0, 22·5, 22·5, 20·0, 20·0, 20·0	Slowing and prolonged *P-R.*
6	*A-V* node, 18·0, 18·0, 17·5	R.V. 97	17½	*As.* **19·5**, **32·0**, **48·0**, **6·0**, **33·5**, **30·0** *Vs.* 19·5, 34·0, **44·0**,　　**43·5**, 30·0	Slowing, escape of auricle and ventricle.
Left 7	*Vagus cut.* Normal, 17·0, 17·0, 16·5	L.V. 87	17½	*As.* **17·0**, **19·5**, **19·5**, **20·0**, **20·0**, **20·0**, **18·5**, **19·0** *Vs.* 17·0, 19·5, 20·0,　　**39·5**, 20·0, 18·5, 19·0	Slowing, prolonged *P-R* ; and one missed beat.
8	*A-V* node, 18·5, 19·0	L.V. 73	17½	*As.* 18·5, **31·5**, **29·0**, **28·5**, **28·0**, **28·0** *Vs.* 18·5, **33·0**, 29·5, 28·5, 28·0, 28·0	Slowing ; escape of auricle. prolonged *P-R.*
9	*A-V* node, 25·0, 25·0	L.V. 120	17½	*As.* **31·0**, **30·0**, **30·0**, **30·0**, **30·0**, **29·5** *Vs.* 32·5, 30·0, 30·0, 30·0, 30·0, 29·5	Slowing and escape of auricle.
10	Normal, 19·0, 19·0, 19·0	L.V. 127	17½	*As.* **21·0**, **22·0**, **22·0**, **22·5**, **22·5**, **23·0**, **22·0** *Vs.* 21·0, 22·0, 22·0, 23·0, 22·5, 23·0, 22·0	Simple slowing and prolonged *P-R.*

Summary. During the *S-A* rhythm, the right and left vagus produced simple slowing with prolongation of the *P-R* interval. During the *A-V* rhythm, both right and left vagi produced greater slowing than during the normal rhythm ; early escape of *S-A* rhythm was seen on all occasions.
　* Twenty-fifths of seconds.
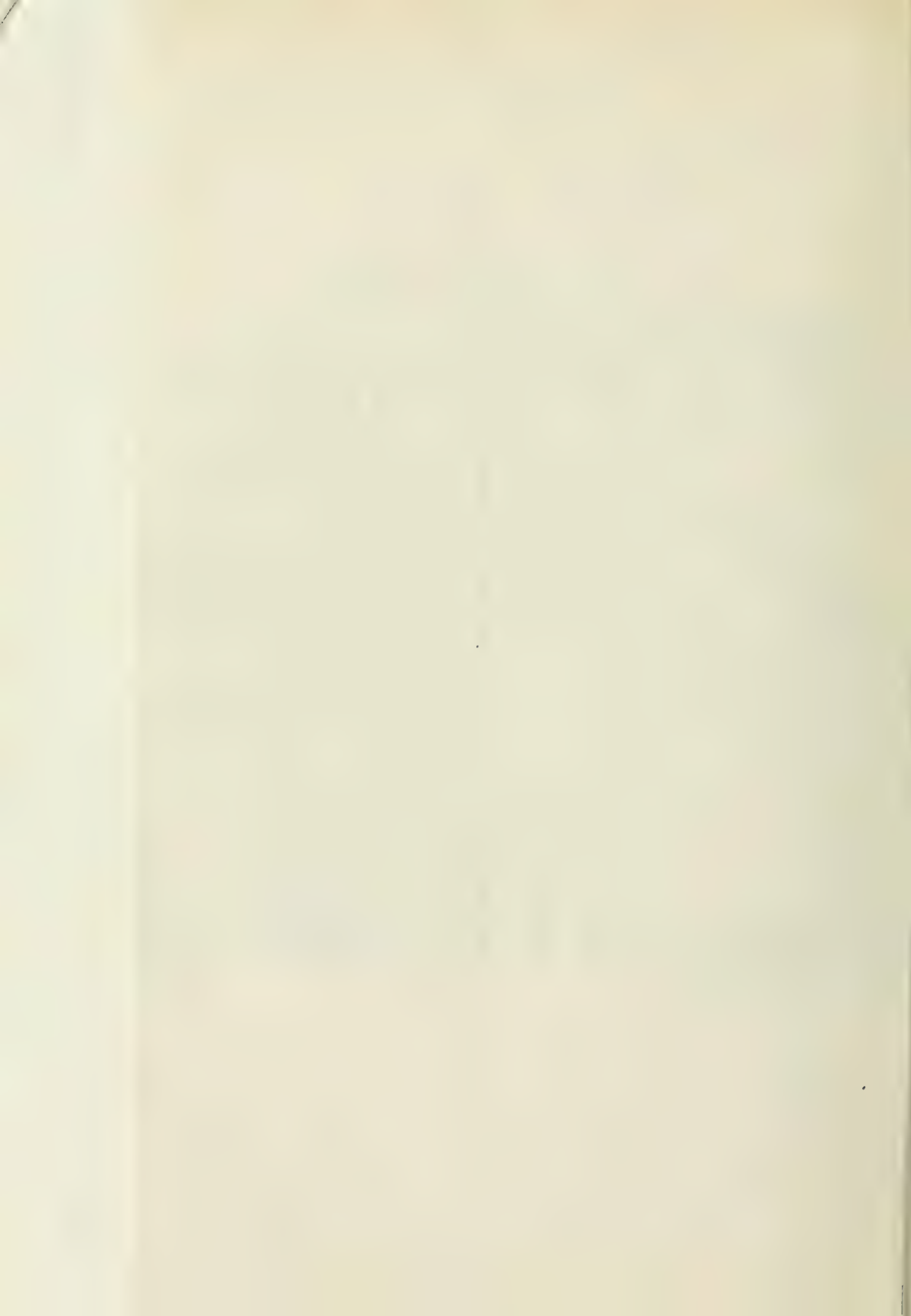
TABLE II.   (DOG ED.)

bs.	Rhythm and rate before stimulation.	Nerve and length of stimulation.	Coil at cm.	EFFECT.	REMARKS.
1	*Right Vagus cut.* Normal ($P \cdot R = \cdot086$ sec.) 13·6, 13·4, 13·2	R.V. 35	22	*As.* **17·0, 18·4, 18·0, 17·2, 15·0** *Vs.* 17·0, 18·4, 18·0, 17·2, 15·0	Simple slowing of the whole heart.
2	*A-V node* ($P \cdot R = \cdot029$ sec.) 14·2, 14·2	R.V. 32	22	*As.* 17·0, 30·0, 22·5, **19·5** *Vs.* 17·0, 30·0, 22·5, 21·0	Slowing; slight reduction of *P-R*; single escape of *S-A* node.
3	Normal, 13·8, 13·9	R.V. 33	22	*As.* **16·5, 20·5, 20·0, 18·0, 17·0** *Vs.* **16·0,** 21·0, 20·0, 18·0, 17·0	Single ventricular escape; slowing.
4	Normal, 13·5, 13·5	R.V. 105	22	*As.* 15·6, **64·0, 44·5** *Vs.* 15·6, 64·0, 44·5	Simple profound slowing.
5	*A-V node,* 15·0, 15·0, 15·0	R.V. 90	22	*As.* 124·0 *Vs.* 124·0	Standstill.
6	*A-V node,* 16·5, 16·0, 16·0	R.V. 70	23	*As.* 17·0, 19·0, 22·5, 21·0, 20·5, 20·0 *Vs.* 17·0, 19·0, 22·5, 21·0, 20·5, 20·0	Simple slowing; very slight reduction of *P-R*.
7	Normal, 15·0, 15·0, 15·0	R.V. 77	23	*As.* **17·0, 17·5, 17·0, 19·0, 19·5, 9·0, 16·5, 16·0** *Vs.* **16·0, 16·5, 17·5, 19·0, 20·0,** 9·5, 16·5, 16·0	Simple slowing with escape of ventricle.
8	*Left Vagus cut.* Normal, 14·0, 14·0	L.V. 70	23	*As.* **16·0, 16·0, 16·0, 16·0, 16·0, 15·5, 16·0, 16·0,** *Vs.* 16·0, 64·0, 31·5, 16·0, *As.* **16·0, 15·0, 15·0** *Vs.* 16·0, 15·0, 15·0	Slowing and four missed beats.
9	Normal, 14·5, 14·0	L.V. 90	22	*As.* **17·0, 16·0, 17·0, 16·5, 17·5, 16·5, 17·0, 17·0,** *Vs.* 17·0, 68·0, 32·5, *As.* **17·0, 16·0, 16·0, 15·5** *Vs.* 34·0, 16·0, 16·0, 15·5	Slowing and five missed beats.
10	*A-V node,* 16·0, 16·0, 16·0	L.V. 90	22	*As.* **21·0, 32·5, 35·0, 33·0, 25·0, 23·0, 22·5, 22·5,** *Vs.* 25·0, 67·5, 32·0, 25·0, 23·0, 22·5, 22·5, *As.* **22·0, 22·0** *Vs.* 22·0, 22·0	Slowing and immediate escape of *S-A* node; one missed beat.
11	*A-V node,* 17·0, 17·0	L.V. 90	22	*As.* 17·0, **34·0, 32·5, 21·0**+ *Vs.* 17·0, 86·0+	Slowing; escape of *S-A* node; two missed beats.
12	Normal, 16·5, 16·5	L.V. 90	22	*As.* **20·0, 25·0, 28·0, 27·0** *Vs.* 20·5, 53·0, 26·5	Slowing; one missed beat.
13	*A-V node,* 16·0, 16·5	R.V. 95	22	*As.* 16·5, **102·5** *Vs.* 16·5, **104·0**	Standstill; escape of *S-A* node.
14	Normal, 15·5, 16·0	R.V. 110	22	*As.* **17·0, 27·0, 90·0** *Vs.* 17·0, 27·5, 90·0	Slowing and standstill; prolonged *P-R*.
15	Normal, 15·0, 15·0	R.V. 90	22	*As.* **100·0, 27·5, 19·5, 18·0, 18·0** *Vs.* 100·0, 27·5, 19·5, 18·0, 18·0	Standstill and slowing; slightly prolonged *P-R*.
16	*A-V node,* 16·5, 16·5, 16·5	R.V. 90	22	*As.* 17·0, 124·0, 34·0, **34·5** *Vs.* 17·0, 124·0, 34·0, 36·0	Standstill, slowing, reduction of *P-R*, and final escape of *S-A* node.

Summary. During the normal rhythm, the right vagus produced far more auricular slowing than the left; the left vagus gave heart-block. During the *A-V* rhythm, the right vagus produced greater slowing than the left vagus, and a reduction of the *P-R* interval, but with the latter there was always an immediate escape of the *S-A* node.

TABLE III. (DOG EL, BOTH VAGI CUT.)

Obs.	Rhythm and rate before stimulation.	Nerve and length of stimulation.	Coil at cm.	Effect.	Remarks.
1	Normal (*P-R* = ·094 sec.) 7·5, 7·5	R.V. 85	21	*As.* **10·0, 10·0, 10·0, 12·0, 12·5, 13·5, 19·5, 16·0,** *Vs.* 10·0, 10·0, 10·5, 12·0, 12·5, 13·5, 19·5, 16·0, *As.* **12·5, 10·0, 10·5, 9·5, 9·0, 8·5, 8·0, 7·5** *Vs.* 12·5, 10·0, 10·5, 9·5, 9·0, 8·5, 7·5, 7·5	Slowing with slight prolongation of *P-R* interval.
2	*A-V* node (*P-R* = ·016 sec.) 10·5, 10·5, 10·5, 10·5	R.V. 85	21	*As.* 12·0, 15·0, 21·0, 52·5, 20·0, 15·0, 14·0, 14·0, *Vs.* 11·5, 15·0, 23·0, **50·0,** 22·0, 15·0, 14·0, 14·0, *As.* 13·5 *Vs.* 13·5	Slowing, reduction of *P-R*, escape of *S-A* node and single escape of ventricle.
7	Normal, 7·5, 7·5, 7·5	L.V. 80	21	*As.* **7·5, 8·5, 9·5, 10·0, 10·5, 11·5, 11·0, 12·0,** *Vs.* 7·5, 8·5, 9·5, 10·5, 11·0, 11·5, 11·5, *As.* **12·5, 12·5, 11·5, 10·0, 10·0, 9·5, 9·0, 8·5** *Vs.* 23·0, 12·5, 11·5, 10·0, 10·0, 9·5, 9·0, 8·5	Slowing of auricle, prolonged interval and dropped beat.
8	*A-V* node, (*P-R* = ·036 sec.) 11·0, 11·0, 11·0	L.V. 70	21	*As.* 11·0, 12·0, 13·0, **12·5, 13·0, 13·0,** 12·5, 12·5, *Vs.* 11·0, 11·5, 13·0, 15·0, 13·0, 13·0, 12·5, 12·5, *As.* 13·0, 12·5, **12·5, 12·5, 12·5, 12·5** *Vs.* 13·0, 12·5, 12·5, 12·5, 12·5, 12·5	Slowing, reduction of *P-R*, escape of *S-A* node and maintenance of this action.
9	Normal, 7·5, 7·5, 7·5, 7·5	L.V. 190+	21	*As.* **8·0, 9·5, 9·5, 10·0, 10·0, 10·5, 10·5, 11·0,** *Vs.* 8·0, 9·5, 9·5, 10·5, 10·0, 11·0, 10·5, 11·0, *As.* **11·5, 12·0, 12·0, 12·5, 12·0, 12·5, 12·0, 12·5** *Vs.* 11·5, 12·0, 12·0, 12·5, 12·0, 12·5, 12·0, 12·5	Slowing, with prolongation of *P-R* interval.
10	*A-V* node (*P-R* = ·036 sec.) 10·5, 11·0, 10·5	L.V. 190+	21	*As.* 11·0, 12·0, 12·5, 14·0, **12·5, 13·0, 13·5, 13·5,** *Vs.* 11·0, 12·0, 12·5, 14·0, 15·0, 12·0, 13·5, 13·5, *As.* **13·5, 13·0, 13·5, 13·5, 13·0, 13·5** *Vs.* 13·5, 13·0, 13·5, 13·5, 13·0, 13·5	Slowing; reduction of *As-Vs*; escape of *S-A* node; maintenance of slowing.
11	Normal, 8·0, 8·0, 8·0	R.V. 210+	21	*As.* **8·5, 11·0, 11·5, 14·5, 19·0, 28·0, 29·5, 26·0·** *Vs.* 8·5, 11·0, 11·5, 15·0, 19·5, 28·0, 29·5, 26·0, *As.* **35·0** *Vs.* 35·0	Profound slowing; slight increase of *P-R* interval.
12	*A-V* node (*P-R* = ·036 sec.) 11·0, 11·0, 11·0, 11·0	R.V. 170+	21	*As.* 11·0, 12·0, 14·0, 16·5, **16·0, 17·0, 18·0, 20·0,** *Vs.* 11·0, 12·0, 14·0, 16·5, 18·0, 17·0, 18·0, 20·0, *As.* **22·0, 30·0+** *Vs.* 22·0, 30·0+	Slowing; reduction of *As-Vs*; escape of *S-A* node; further slowing.
13	Normal 8·0, 8·0, 8·0, 8·0	R.V. 160+	20	*As.* **8·0, 12·0, 16·0, 32·0, 52·0, 44·0+** *Vs.* 8·0, 12·0, 16·0, 32·0, 52·0, 44·0+	Profound slowing with very slight prolongation of *P-R* interval.
14	*A-V* node (*P-R* = ·036 sec.) 11·0, 11·0, 11·0	R.V. 170+	20	*As.* 12·5, 17·0, **17·5, 29·0, 96·0+** *Vs.* 12·5, 17·0, 19·0, 29·0, 96·0+	Slowing; slight reduction of *P-R*; escape of *S-A* node; profound slowing and standstill.
15	Normal, 7·5, 7·5, 7·5, 7·5	L.V. 175+	20	*As.* **8·0, 10·0, 10·0, 10·0, 10·0, 11·0, 11·5, 12·5,** *Vs.* 8·0, 10·0, 10·5, 10·5, 10·0, 11·0, 12·0, 12·5, *As.* **14·0, 14·0, 13·5, 13·5, 13·5, 13·5, 13·0** *Vs.* 27·0, 27·0, 27·0, 26·5	Slowing; prolonged *P-R* interval; 2 : 1 heart-block
16	*A-V* node (*P-R* = ·036 sec.) 12·0, 12·0, 11·5	L.V. 180+	20	*As.* 12·0, **15·5, 14·0, 14·0, 14·5, 15·0, 16·0, 15·0,** *Vs.* 12·0, 17·0, 14·0, 15·0, 15·5, 15·0, 16·0, 15·0, *As.* **30·0, 30·0** *Vs.* 28·0, 30·0	Slowing; escape of *S-A* node and subsequent slowing with prolonged *P-R* interval.
S-A 35	Node Clamped. *A-V* node (*P-R* = ·016 sec.) 12·5, 12·5, 12·5	R.V. 150+	20	*As.* 12·5, 13·0, 14·0, 15·0, 16·5, 18·0, 19·5, 20·0 *Vs.* 12·5, 13·0, 14·0, 15·0, 16·5, 18·0, 19·5, 20·0	Slowing; with slight reduction of *P-R*.
36	*A-V* node (*P-R* = ·016 sec.) 13·0, 13·0, 13·0	L.V. 150+	20	*As.* 14·0, 14·5, 16·0, 16·5, 18·0, 19·0, 21·0, 22·5 *Vs.* 14·0, 14·5, 16·0, 16·5, 18·0, 19·0, 21·0, 22·4	Slowing; with slight reduction of *P-R*.
37	*A-V* node (*P-R* = ·016 sec.) 12·5, 12·5	L.V. 170+	20	*As.* 12·5, 13·0, 13·0, 13·5, 15·0, 15·0, 15·5, 16·5, *Vs.* 12·5, 13·0, 13·0, 14·0, 15·0, 15·0, 15·5, 16·5, *As.* 17·5, 18·0, 18·5 *Vs.* 17·5, 18·0, 18·5	Slowing; with slight reduction of *P-R*.
38	*A-V* node (*P-R* = ·016 sec.) 14·0, 14·0	R.V. 160+	20	*As.* 14·0, 155·0+ *Vs.* 14·0, 155·0+	Standstill.

Summary. During the *S-A* rhythm, the right nerve slowed the auricle much more than the left; the left produced a greater degree of apparent heart-block. After abolishing the *S-A* rhythm by cooling (and during *A-V* rhythm) both nerves produced slowing, the right especially, with reduction of *P-R* interval; and eventually there was escape of the *S-A* node (under right and left-sided inhibition) and subsequent slowing of the whole heart (with the right especially). After clamping the *S-A* node, both nerves produced slowing of the *A-V* rhythm; the right more especially; both also produced reduction of *P-R* interval.

TABLE IV. (DOG EG.)

Obs.	Rhythm and rate before stimulation.	Nerve and length of stimulation.	Coil at cm.	EFFECT.	REMARKS.
Right Vagus cut.					
1	Normal (P-R=·103 sec.) 12·0, 12·0	R.V. 87	20	As. **13·0, 15·5, 65·0, 24·0, 19·0, 14·5, 12·5, 12·0,** Vs. 13·0, 16·0, 64·5, 24·0, 19·0, 14·5, 12·5, 12·0, As. **12·0, 12·0** Vs. 12·0, 12·0	Prolonged P-R; standstill.
2	A-V node (P-R=·025 sec.) 14·0, 14·0	R.V. 60	20	As. **15·0, 17·0, 50·0, 22·0, 21·5, 21·5, 21·0, 20·5,** Vs. 17·5, 17·0, 50·0, 22·0, 21·5, 21·5, 21·0, 20·5, As. **20·0** Vs. 20·0	Escape of S-A node; slowing; later stoppage.
Left Vagus cut.					
3	Normal, 12·0, 12·0, 12·0	L.V. 90	16½	As. **12·5, 13·0, 13·0, 13·0, 13·5, 13·0, 12·5, 12·5,** Vs. 12·5, 13·0, 13·5, 13·0, 13·5, 13·0, 12·5, 12·0, As. **12·0, 12·0, 12·0** Vs. 12·0, 12·0, 12·0	Slight slowing and slight prolongation of P-R.
5	A-V node, 15·0, 14·5, 14·5	L.V. 200	16½	As. 15·0, 15·0, 15·5, 19·0,* 16·5,* 16·0,* 16·0,* Vs. 15·0, 15·0, 15·0, 20·5, 16·5, 16·0, 16·0, As. 16·0,* 16·5,* 16·5,* 17·0,* 16·5* Vs. 16·0, 16·5, 16·5, 17·0, 16·5	Slight slowing and reduced P-R; later greater slowing and escape of new point.* (As- Vs ·06 sec.).
6	Normal, 12·0, 12·0, 12·5	L.V. 200	16½	As. 12·5, 14·0, 13·5, 14·0, 14·0, 14·5, 15·0, 15·0, Vs. 12·5, 14·0, 13·5, 14·0, 15·0, 14·5, 15·0, 15·0, As. **15·5, 16·0, 16·5, 16·5, 16·0** Vs. 15·5, 16·0, 16·5, 16·5, 16·0	Slight slowing and prolongation of the P-R interval.
7	Normal, 12·0, 12·0, 12·0	R.V. 275	16½	As. **14·0, 15·0, 30·0, 69·0, 59·5, 72·0** Vs. 14·0, 15·0, 30·0, 69·0, 59·5, 72·0	Profound slowing and standstill, with prolonged P-R.
S-A node clamped.					
10	A-V node (As-Vs=·032 sec.) 18·0, 18·0	R.V. 90	16½	As. 18·5, 21·5,* 104·5, 34·0 Vs. 18·5, 27·0, 99·0, 34·0	Slowing; escape of auricle from new point with response of ventricle*; standstill; A-V rhythm with reduced P-R.
11	A-V node, 19·5, 19·5	L.V. 125	16½	As. 55·5, 36·0, 36·5, 35·0 Vs. 55·5, 36·0, 36·5, 35·0	Standstill and profound slowing, with reduced P-R.
12	A-V node, 18·5, 18·5	L.V. 75	18	As. 22·0,* 44·0, 32·5, 34·0, 34·0 Vs. 28·5, 38·0, 32·5, 34·0, 34·0	Profound slowing. Single escape of auricle from new point with response of ventricle.*

Summary. Stimulation of right vagus had much more profound effect than left on normal rhythm (left produced very slight slowing and altered conduction interval). During A-V rhythm, right vagus produced great slowing and escape of S-A rhythm; left produced less slowing and escape of new auricular centre. After breaking up the S-A node by clamping, both R.V. and L.V. produced profound slowing of A-V rhythm, the right nerve more especially; both produced reduction of P-R interval.

TABLE V. (Dog EK, both vagi cut.)

Obs.	Rhythm and rate before stimulation.	Nerve and length of stimulation.	Coil at cm.	Effect.	Remarks.
1	Normal, ($P\text{-}R = \cdot092$ sec.) 11·0, 11·0, 11·0	R.V. 105	22	*As.* **12·0, 13·0, 14·0, 14·0, 15·0, 15·5, 16·0, 16·5,** *Vs.* 12·5, 41·0, 30·5, 32·5, *As.* **16·0, 14·5, 14·0, 13·5, 12·5** *Vs.* 16·0, 14·5, 13·5, 13·5, 12·5	Partial heart-block, and slowing of auricle.
2	Ectopic, ($P\text{-}R = \cdot089$ sec.) Pinvert. 16·0, 16·0	R.V. 130	22	*As.* 16·5, 16·5, 16·0, 16·0, 16·0, 16·0, 17·0, 17·0, *Vs.* 16·5, 32·5, 32·0, 33·0, *As.* 16·0, 16·5, 17·0 *Vs.* 33·0, 16·5, 17·0	Partial heart-block; little or no slowing of auricle.
3	Normal	L.V. 140	22	Little or no effect.	
4	Normal, 10·5, 10·5, 10·5	L.V. 110	20	*As.* **12·0, 13·0, 13·0, 12·5, 13·0, 13·0, 13·0, 13·5,** *Vs.* 12·0, 13·0, 25·5, 38·5, *As.* **14·0, 14·0, 13·5, 13·5, 13·0, 13·0, 12·0** *Vs.* 27·5, 27·5, 13·5, 13·0, 13·0, 12·0	Partial heart-block and slowing of auricle.
5	Ectopic, 17·5, 17·5	L.V. 145	20	*As.* 18·0, 21·0, 22·5, 24·0, 26·5, 29·0, 30·0, 31·5, *Vs.* 18·0, 21·0, 22·5, 24·0, 26·5, 29·0, 30·0, 31·5, *As.* 32·0 *Vs.* 32·0	Simple slowing with slight prolongation of $P\text{-}R$ interval
6	Normal, 11·0, 11·0, 11·0	R.V. 115	20	*As.* **13·5, 14·0, 18·0, 21·5, 30·0, 27·5, 19·5, 16·0,** *Vs.* 47·0, 98·5, 16·0, *As.* **15·0, 15·0, 15·0, 14·5, 14·0** *Vs.* 15·0, 15·0, 15·0, 14·5, 14·0	Considerable slowing and partial heart-block.
7	Ectopic, 19·5, 19·5	R.V. 125	20	*As.* 19·5, 27·5, 28·0, 31·0, 36·5, 26·5 *Vs.* 19·5, 58·0, 91·5	Considerable heart-block and slowing of auricle.
8	Normal, 11·0, 11·0	R.V. 215+	20	*As.* **15·0, 13·5, 15·0, 15·5, 15·0, 18·0, 26·0, 24·0,** *Vs.* 29·0, 30·0, 85·0, *As.* **26·0, 26·5, 20·0+**	Slowing of auricle and considerable partial heart-block.
9	Ectopic, 19·0, 19·0, 19·0	R.V. 190+	20	*As.* 19·0, 19·0, 19·0, 18·5, 18·0, 18·0, 18·5, 18·5, *Vs.* No ventricular contraction. *As.* 19·0, 18·5	No slowing of auricle; high grade of heart-block.
10	Normal, 11·0, 11·0	L.V. 195+	20	*As.* **11·5, 13·0, 13·0, 13·0, 13·5, 13·5, 14·0, 14·5,** *Vs.* 11·5, 13·0, 14·5, 55·0, *As.* **14·0, 14·0, 14·0, 15·0, 14·5, 15·0,** &c. *Vs.* 27·5, 28·0, 29·5	Slowing of auricle and partial heart-block.
11	Ectopic, 16·5, 16·0, 16·0	L.V. 190+	20	*As.* 14·5, 17·5, 17·0, 17·5, 20·0, 23·0, 24·0, 24·5, *Vs.* 14·5, 17·5, 17·5, 18·0, 20·0, 23·0+, 24·0, 24·5, *As.* 24·5, 25·0, 25·0 *Vs.* 24·5, 25·0, 25·0	Slowing of whole heart and prolonged $P\text{-}R$.
S-A 12	node clamped A-V node ($P\text{-}R = \cdot024$ sec.) 19·0, 19·0, 19·0	L.V. 150+	20	*As.* 19·0, 46·5, 42·5, 42·0 *Vs.* 19·0, 44·0,* 42·5,* 42·0*	Profound slowing; escape of left type of Us^*; (interval $Vs\text{-}As = \cdot076$ sec.).
13	A-V node ($P\text{-}R = \cdot022$ sec.) 19·0, 19·0	R.V. 190+	20	*As.* 65·0, 86·0 *Vs.* **62·5,*86·0***	Profound slowing; escape of right type of Vs^*; (interval $Vs\text{-}As = \cdot074$ sec.).
14	A-V node, 18·0, 18·0	R.V. 180+	21	*As.* 56·0, 59·0, 60·0 *Vs.* **54·0,* 59·0,* 60·0***	Profound slowing; escape of right type of Vs^*; ($Vs\text{-}As = \cdot073$ sec.).
15	A-V node, 18·0, 18·0	L.V. 180+	21	*As.* 44·5, 40·5, 39·5, 40·0 *Vs.* **42·5,* 40·5,* 39·5,* 40·0***	Profound slowing; escape of left type of Vs^*; ($Vs\text{-}As = \cdot078$ sec.).
16	A-V node, 17·5, 17·5	R.V. 205+	22	*As.* 18·0, 26·0,* 28·5,* 57·5,* 55·0+ *Vs.* 18·0, 28·0, 28·5, 57·5, 55·0+	Profound slowing; escape of new auricular centres.*
17	A-V node, 16·5, 16·5	L.V. 190+	22	*As.* 17·5, 19·0, 20·5, 23·0, 25·5, 28·5, 50·0+ *Vs.* 17·5, 19·0, 20·5, 23·0, 25·5, 28·5, 50·0+	Gradual profound slowing of whole heart; slight prolongation of $P\text{-}R$ interval.

Summary. During the *S-A* rhythm, both nerves produced slowing of auricle, the right in greater degree. Both produced partial heart-block, the right again being more effective. After abolishing the *S-A* rhythm by cooling (production of rhythm from ectopic focus with very slight reduction of $P\text{-}R$ time), the effect of right and left nerves on the new centres was definite but slight (on two occasions there was no reaction to the right nerve); partial heart-block was produced by the right, on the left side this effect was but slight.

After clamping the *S-A* node, an *A-V* rhythm became established. Both nerves then produced profound slowing, the right being always the more effective, and on one occasion leading to escape of the auricle from other foci.

TABLE VI. (Dog EM, BOTH VAGI CUT.)

Obs.	Rhythm and rate before stimulation.	Nerve and length of stimulation.	Coil at cm.	Effect.	Remarks.
1	Normal ($P\text{-}R = \cdot087$ sec.) 7·5, 7·5, 7·5	R.V. 190	22	*As.* **10·0, 23·0, 19·5, 22·0, 22·0, 27·0, 23·0** *Vs.* 10·0, 23·0, 19·5, 22·0, 22·0, 27·0, 23·0	Profound slowing; prolonged *P-R*.
2	*A-V* node ($P\text{-}R = \cdot023$ sec.) 10·0, 10·0, 10·0, (*As- Vs* secs.)	R.V. 210	22	*As.* 205·0+ *Vs.* 205·0+	Prolonged standstill.
3	Normal, 7·5, 7·5, 7·5	R.V. 195	22	*As.* **11·5, 37·5, 24·0, 25·0, 25·0, 21·5, 30·0** *Vs.* 11·5, 37·5, 24·0, 25·0, 25·0, 21·5, 30·0	Profound slowing; prolonged *P-R*.
4	*A-V* node, 10·5, 10·5, 10·5	R.V. 200	22½	*As.* 15·0,* 60·0, 100·0 *Vs.* 16·5, **54·0†** **100·0†**	Slowing; escape of auricle from new focus*; standstill; escape of ventricle † auricle following it.
6	Normal, 7·0	L.V. 195	22	*As.* **8·0, 9·5, 9·0, 9·0, 9·5, 10·0, 10·0, 9·5, 9·5,** *Vs.* 8·0, 10·0, 9·5, 9·0, 9·5, 10·0, 10·0, 9·5, 9·5, *As.* 10·0,* 10·0,* 9·5,* 9·5,* 9·5,* 9·5,* 9·5,* *Vs.* 10·0, 10·0, 9·5, 9·5, 19·0, 10·0, *As.* 9·5,* 9·5,* 9·5,* 9·5,* *Vs.* 18·5, 19·0	Slight slowing and prolonged *P-R* interval; sudden escape of auricle from new centre* (invert *P*); further heart-block.
7	*A-V* node, 10·5, 10·5, 10·5, 10·5	L.V. 180	22	*As.* 12·5, 14·0,* 12·5,* 12·5,* 12·5,* 13·0,* 13·5,* *Vs.* 12·5, 15·0, 13·5, 12·5, 12·5, 13·0, 13·5, *As.* 13·5,* 13·5,* 14·0,* 14·0,* 14·0,* 14·5* *Vs.* 13·5, 13·5, 14·0, 14·0, 14·0, 14·5	Slowing; escape of auricle from new point; *P* seen as inverted complex similar to that of last observation*; *P-R* prolonged.
8	Normal, 7·0, 7·0, 7·0	L.V. 185	22	*As.* **7·0, 9·5, 9·5, 9·0, 9·0, 9·5, 9·5, 9·5, 9·5, 9·5,** *Vs.* 7·0, 9·5, 9·5, 9·5, 9·5, 9·5, 9·5, 9·5, 9·5, 9·5, *As.* **9·5, 9·5, 9·5, 9·5, 9·5, 9·5, 9·5, 9·5, 9·5** *Vs.* 9·5, 9·5, 9·5, 9·5, 9·5, 9·5, 9·5, 9·5, 9·5	Very slight slowing and pro-longation of *P-R* interval.
9	*A-V* node, 10·5, 10·5, 10·5	L.V. 190	22	*As.* 11·5, 12·5, 14·5, 13·5,* 13·5,* 13·5,* 14·0,* *Vs.* 11·5, 12·5, 14·5, 15·0, 13·5, 13·5, 14·0, *As.* 14·0,* 14·0,* 14·0,* 14·5,* 14·5* *Vs.* 14·0, 14·0, 14·0, 14·5, 14·5	Slowing; sudden escape of auricle; *P* appears inverted*; prolonged *P-R*.
10	Normal, 7·0, 7·0, 7·0, 7·0	L.V. 90	21	*As.* **7·0, 8·5, 9·0, 9·5, 9·0, 9·0, 8·5, 8·5, 9·5, 9·5,** *Vs.* 7·0, 8·5, 9·5, 9·5, 18·0, 17·0, 19·0, *As.* **9·5, 9·5, 9·5, 9·5, 9·5, 9·5, 9·5, 9·5, 9·5, 9·5** *Vs.* 19·0, 19·0, 19·0, 19·0, 19·0	Very slight slowing; 2 : 1 heart-block.
11	*A.-V* node, 10·0, 10·0, 10·0	L.V. 185	21	*As.* 10·0, 14·0, 16·5, 15·0,* 13·0,* 17·0,* 16·0,* *Vs.* 10·0, 14·0, 16·5, 16·5, 13·0, 17·0, 16·0, *As.* 13·5,* 17·0,* 16·0,* 14·5,* 14·0* *Vs.* 13·5, 17·0, 16·0, 14·5, 14·0	Slowing; reduction of *P-R*; escape of auricle; *P* appears inverted*; *P-R*. prolonged.

Summary. During the *S-A* rhythm, the right nerve slowed the auricle much more than the left; the left produced a greater apparent degree of heart-block.

After abolishing the *S-A* rhythm by cooling both nerves produced slowing of *A-V* rhythm (the right much more so than the left and leading on one occasion to standstill). When the left nerve was stimulated, the impulses seemed to spring from a new centre often times and 2 : 1 heart-block often developed.

TABLE VII. (DOG EF.)

Obs.	Rhythm and rate before stimulation.	Nerve and length of stimulation.	Coil at cm.	EFFECT.	REMARKS.
Right Vagus cut. 2	Normal ($P\text{-}R = \cdot091$ sec.) 8·5, 8·5, 8·5	R.V. 89	16	As. 10·0, 11·0, 9·5, 10·0, 10·0, 11·0, Vs. 9·5, 9·0, 9·5, 9·5, 10·0, 10·0, 10·5, 11·0, As. 27·5, 24·0, 15·0, 13·0, 12·5, 12·0, 11·5, Vs. 9·5, 14·5, 9·5, 14·0, 13·0, 12·5, 12·0, 11·5, As. 11·0 Vs. 11·0	Escape of A-V node; slowing; reduced P-R; suppression of auricle; ventricle continuing; return of S-A beats; long P-R and response of ventricle.
3	Normal, 10·0, 10·0	R.V. 70	19	As. 10·0, 13·0, 11·0, 11·0, 11·5, 11·5, 12·0, 12·0, Vs. 10·0, 11·0, 11·0, 11·0, 11·5, 11·5, 12·0, 12·0, As. 11·5, 11·5, 11·5, 11·5, 11·5, 10·5, 10·0, 10·0 Vs. 11·5, 11·5, 11·5, 11·5, 11·5, 11·5, 11·0, 10·0	Slowing; escape of A-V node; slowing of same with reduced P-R; return of S-A beats.
4	A-V node, ($P\text{-}R = \cdot029$ sec.) 10·0, 10·0	R.V. 105	19	As. 10·0, 10·0, 10·0, 10·0, 10·0, 10·0, 10·0, 10·0, Vs. 10·0, 10·0, 10·0, 10·0, 10·0, 10·0, 10·0, 10·0, As. 10·5, 11·0, 11·0, 11·0, 11·0, 11·0, 10·5, 10·5, Vs. 10·5, 10·0, 11·0, 11·0, 11·0, 11·0, 10·5, 10·5, As. 10·5, 10·5 Vs. 10·5, 10·5	Simple delayed slowing (slight) with reduced P-R.
Left 5	*Vagus cut.* Normal, 8·5, 8·5, 8·5	L.V. 72	19	As. 8·5, 8·5, 8·5, 9·0, 10·0, 11·0, 11·0, 11·5, 11·0, Vs. 8·5, 8·5, 8·5, 9·5, 10·0, 11·0, 11·0, 11·5, 11·0, As. 10·0, 9·0, 9·0, 8·5, 8·5, 8·5 Vs. 10·0, 9·0, 8·5, 8·5, 8·5, 8·5	Simple slowing with slight prolongation of P-R interval.
6	A-V node, 10·0, 10·0	L.V. 90	19	As. 10·5, 10·5, 11·0, 11·0, 10·5, 11·0, 11·0, 11·5, 12·0 Vs. 10·5, 10·5, 11·0, 11·0, 10·5, 11·0, 11·0, 11·5, 12·0 As. 12·0, 12·0, 11·5, 11·0, 11·5, 11·0, 11·0, 11·0 Vs. 12·0, 12·0, 11·5, 11·0, 11·5, 11·0, 11·0, 11·0	Simple slowing (slight) with reduced P-R.
Electrodes Interchanged. 7	Normal, 9·5, 9·5, 9·5, 9·5	L.V. 175+	16	As. 9·5, 10·0, 10·0, 11·5, 12·0, 12·5, 13·0, 13·5, Vs. 9·5, 10·0, 10·0, 11·5, 12·0, 12·5, 13·0, 13·5, As. 14·5, 15·0, 15·0, 15·5, 16·0 Vs. 14·5, 15·0, 15·0, 15·5, 16·0	Simple slowing continuing throughout stimulation.
8	A-V node, 11·5, 11·5	L.V. 200+	16	As. 11·5, 11·5, 11·5, 12·5, 13·0, 14·0, 15·0, 16·0, Vs. 11·5, 11·5, 11·5, 12·5, 13·0, 14·0, 15·0, 16·0, As. 18·5, 20·5, 29·5, 27·0 Vs. 18·5, 20·5, 31·5, 27·0	Slowing; reduction of P-R; escape of S-A node during stimulation.
9	A-V node, 12·0, 12·0, 12·0	L.V. 180+	16	As. 12·0, 12·5, 12·5, 13·5, 14·5, 16·0, 15·5,* Vs. 12·0, 12·5, 12·5, 13·5, 14·5, 16·0, 17·5, As. 16·0,* 17·5,* 18·5,* 21·0* Vs. 16·0, 17·5, 18·5, 21·0	Slowing, with reduced P-R; escape of auricle from new focus and subsequent slowing ($P\text{-}R = \cdot08$).*
10	Normal, 10·0, 10·0, 10·0	R.V. 190+	16	As. 10·0, 12·0, 14·0, 12·5, 12·5, 12·5, 13·0, 13·5, Vs. 10·0, 12·0, 12·5, 12·5, 12·5, 12·5, 13·0, 13·5, As. 14·0, 15·0, 15·5, 16·5, 17·5 Vs. 14·0, 15·0, 15·5, 16·5, 17·5	Slowing; escape of A-V node and subsequent slowing with reduction of P-R.
11	A-V node, 12·5, 12·5	R.V. 190+	16	As. 12·5, 12·5, 12·5, 12·5, 13·1, 12·6, 13·1, 13·1, Vs. 12·5, 12·5, 12·5, 12·5, 13·0, 12·5, 13·0, 13·0, As. 13·6, 14·1, 14·5, 15·0, 15·0, 16·0 Vs. 13·5, 14·0, 14·5, 15·0, 15·0, 16·0	Simple slowing, with very slight and gradual reduction of interval between P and R

Summary. During S-A rhythm the right nerve had more effect on the auricle than the left, and led to escape of the A-V node. No such escape was seen on stimulating the left nerve, even when the coil was closer up.

During A-V rhythm, the left nerve had more effect than the right in producing slowing and led to escape of the S-A node; no such escape was seen on stimulating the right nerve, even when slowing was sufficient. Both nerves gave a reduction of the P-R interval.

TABLE VIII.   (DOG EJ, BOTH VAGI CUT.)

Obs.	Rhythm and rate before stimulation.	Nerve and length of stimulation.	Coil at cm.	EFFECT.	REMARKS.
1	Normal (P-R=·132 sec.) 12·0, 12·5, 12·5	R.V. 87	20	As. 24·0, 29·5 42·0, 20·0, 15·5, 16·5, 15·5, 15·0, Vs. 24·0, 29·5, 42·0, 20·0, 15·5, 16·5, 15·5, 15·0, As. 14·0, 13·5 Vs. 14·0, 13·5	Profound slowing of whole heart.
2	Normal (cooled), 15·5, 15·5, 16·0	R.V. 105	20	Vs. 16·0, 120·0, 27·0 As. 16·0, 120·0, 27·0	Standstill of whole heart.
3	Ectopic (P-R=·074 sec.) 16·0, 16·0, 16·0	R.V. 90	20	As. 69·0,* 47·0, 28·0, 23·0, 20·5, 19·5, 19·0, 18·5 Vs. 65·0,* 52·0, 28·0, 23·0, 20·5, 19·5, 19·0, 18·5	Standstill; single escape of ventricle and S-A node*; then further escape of S-A node.
4	Normal, 13·5, 13·5, 13·5	L.V. 110	20	As. 16·0, 16·0, 18·5, 21·0, 22·0, 23·0, 20·0, 17·5, Vs. 16·0, 16·0, 18·5, 21·0, 22·0, 23·0, 20·0, 17·5, As. 16·5, 15·5 Vs. 16·5, 15·5	Slowing of whole heart.
5	Ectopic, 16·0, 16·0, 16·0	L.V. 100	20	As. 16·5, 20·0, 35·0, 52·0, 26·0, 23·0 Vs. 16·5, 21·5, 35·0, 52·0, 26·0, 23·0	Escape of S-A node and profound slowing.
6	Normal, 14·0, 14·0, 14·0	L.V. 330	20	As. 14·5, 15·0, 16·5, 19·0, 20·5, 22·5, 23·5, 25·0, Vs. 14·5, 15·0, 16·5, 19·0, 20·5, 22·5, 23·5, 25·0, As. 25·5, 26·0, 27·5, 28·0, 29·0, 28·5 Vs. 25·5, 26·0, 27·5, 28·0, 29·0, 28·5	Slowing of whole heart (maintained).
7	Ectopic, 16·0, 16·0, 16·0	L.V. 280	20	As. 17·0, 20·0, 24·0,* 26·0,* 155·0 Vs. 17·0, 20·0, 22·5,* 26·0,* 159·0	Slowing; single escape of A and V; two escapes of new centre; (* As- Vs=0 sec.); standstill; escape of S-A node.
8	Normal, 13·5, 13·5, 13·5	R.V. 280	20	As. 15·5, 16·5, 18·0, 20·5, 22·0, 23·5, 25·0, 25·5, Vs. 15·5, 16·5, 18·0, 20·5, 22·0, 23·5, 25·0, 25·5, As. 25·5, 25·5, 25·5, 26·0 Vs. 25·5, 25·5, 25·5, 26·0	Slowing of whole heart.
9	Ectopic, 16·0, 16·0, 16·0	R.V. 275	20	As. 19·5, 20·5,* 21·5,* 24·0,* 32·5, 40·0, 40·0, Vs. 19·5, 19·0,* 21·5,* 24·0,* 36·0, 40·0, 40·0, As. 40·5 Vs. 40·5	Slowing; single escape of A and V; three escapes of new centre (*As-Vs=0); further slowing, and escape of S-A node.
10	Normal, 14·0, 14·0, 14·0	L.V. 270	20	As. 14·5, 16·0, 17·0, 18·0, 21·5, 22·5, 24·5, 25·0, Vs. 14·5, 16·0, 17·0, 18·0, 21·5, 22·5, 24·5, 25·0, As. 120·0 Vs. 7·5,* 9·0, 6·0, 7·0, 7·5, 7·5, 6·5, 7·5, 6·5, 8·0, 7·0, 8·0, 32·0	Slowing of whole heart; 12 rapid beats from left ventricle*; normal rhythm resumed.
11	Ectopic, 16·0, 16·0, 16·0	L.V. 255	20	As. 17·0, 20·0, 21·5, 31·0, 33·5, 39·0, 40·5, 45·0 Vs. 17·0, 21·0, 21·5, 31·0, 33·5, 39·0, 40·5, 45·0	Slowing; escape of S-A node; further slowing.
12	Normal, 14·0, 14·0, 14·0	L.V. 270	20	As. 14·5, 17·0, 16·5, 17·5, 20·0, 24·5, 24·5, 24·5, Vs. 14·5, 17·0, 16·5, 17·5, 20·0, 24·5, 24·5, 24·5, As. 51·5, 52·5 Vs. 10·0,* 7·0, 6·0, 28·5, 9·0,* 7·5, 35·0, 9·0*	Slowing of whole heart; short runs of rapid beats from left ventricle*followed by normal beats.
13	Ectopic, 17·0, 17·0, 17·0	L.V. 240	20	As. 17·0, 20·5, 21·0, 33·5, 36·0, 42·0, 44·5 Vs. 17·0, 21·5, 21·0, 33·5, 36·0, 42·0, 44·5	Slowing and escape of S-A node; further slowing.

Summary. Both vagi produced simple slowing while S-A rhythm was present, the right nerve having rather the greater effect. During the A-V rhythm, right and left nerve produced slowing and almost immediate escape of the S-A node. The right produced greater slowing but simply because the S-A node was more under its control and its escape was slower. On two occasions, while the normal rhythm was present stimulation of the left vagus gave a ventricular tachycardia. This was not seen under similar circumstances while A-V rhythm was present.

EXPERIMENTAL HEART-BLOCK WITH ATRIO-VENTRICULAR RHYTHM.

By JOHN MEAKINS.*

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THE observations of this paper were undertaken with a twofold object and at the suggestion of Dr. Lewis, who has kindly aided me in carrying out the work. In the first instance, it seemed desirable to devise a simple method of producing various degrees of heart-block without permanently damaging the auriculo-ventricular node or bundle, a method which could be adopted as a simple laboratory routine ; and secondly, to observe the effect of bundle lesions upon the heart while beating in response to a rhythm from the auriculo-ventricular node.

Method.

All the experiments were carried out upon dogs, fully anæsthetised with morphia, chloral and ether. Artificial respiration was performed by the usual intermittent inflation of the lungs. The sternum was split longitudinally and the sides of the chest wall were drawn apart, the pericardium was opened and stitched to the chest wall. Atrio-ventricular rhythm was produced by applying cold over the sulcus terminalis, as described in an accompanying communication by Lewis. In the present series of experiments, it was necessary to cover the descending portion of the lead tubing with rubber in order to obviate its occasional contact with the metal of the clamp during the production of heart-block. In order to obtain varying degrees of impaired conduction through the auriculo-ventricular bundle, it was essential that this structure should not be severed. For this purpose a special heart-clamp was devised, and was constructed for us by Mayer and Meltzer (Fig. 1). The arms of this clamp are 9 centimetres long, and both are curved laterally, so as to form an irregular ellipse. The arm *A* has a curvature of 0·7 centimetres and *B* of 1·4 centimetres. Besides this the blades are bent backwards at an obtuse angle so that the tips are 0·8 centimetres from the straight line. The blade of arm *A* should begin to bend 1·5 centimetres from the tip while that of arm *B* begins slightly lower or about 1 centimetre from the end. The opposing surfaces of the blades are flattened and striated transversely with twenty striæ to the centimetre. The whole clamp is made of tempered steel. The

arms taper slightly, the smallest diameter being about 0·3 centimetres. The blades are a little less than 1 centimetre in length and about 0·4 centimetres in width. The arm marked A is inserted into the left carotid artery a few centimetres above its origin and passed just through the aortic valves into the left ventricle. When the point of the arm is at the aortic ring, care is necessary to prevent its catching in a segment of the aortic valve. Any slight bleeding is easily controlled by a ligature tied about the carotid. The arm marked B is inserted through a small slit in the tip of the right auricle and tied in position by a firm ligature ; as little tissue as possible being injured. The arms being in place, they are jointed together and the clamp as a whole is then placed in position. The curves of the clamp are so arranged that it tends naturally to take the correct position. Otherwise slight adjustment is needed, the right blade being felt through the wall of the right auricle and guided into position during stimulation of the vagus.

Fig. 1.

The arm passing down the carotid should be palpable through the wall at the base of the aorta. When the blades are gently approximated, that in the right auricle should be palpable ventrally, on the line of junction of the right auricle and ventricle, to the central and left side of the coronary sinus. If this be carefully observed the pressure surface of the right blade, when pressed home, will be directed dorsally and will be in apposition with the base of the septal segment of the tricuspid valve. The blade in the left ventricle will be directed ventrally and will be dorsal to the right dorsal cusp of the aortic valve. In applying the blades too far to the right, there is danger of involving the region of the coronary sinus, although this has not occurred in any of the present experiments. On the other hand, by applying the blades too far to the left the bundle may be compressed in the region of its bifurcation. Bundle branch lesions were frequent in the earlier experiments, but for later experiments the curves of the blades have been corrected accordingly. The pressure exerted on the bundle can be most easily regulated by the sense of touch. In fact, by gently regulating the degree of pressure, defects of auriculo-ventricular bundle conduction may be obtained, varying from a lengthened P-R interval

to complete heart-block. When complete heart-block has been produced, through firm pressure, the normal rhythm may return, though some prolongation of the *P-R* interval may remain. If the pressure be very firm or maintained long enough, permanent dissociation results. At the end of the present experiments, the heart was opened with the clamp *in situ* and its exact point of application was identified.

Methods of observation.

The various rhythms and changes from one to another were observed and recorded by means of galvanometric curves. The body current was led from the right shoulder and the left groin by means of copper electrodes sutured beneath the skin. In order to prevent irregularities of the electrocardiographic curves through the application of the fingers to the clamp, the handles of the latter were covered with solid paraffin. This effectually eliminated extraneous currents from this source.

Description of records.

In each experiment, control curves were first taken to test the effect of applying cold to the sulcus terminalis. In the successful experiments, slowing of the whole heart was almost immediately followed by the appearance of *A-V* rhythm. The action of the auricle and ventricle was simultaneous, and in these uncomplicated curves, the *P-R* interval was always positive, varying from ·009 to ·050 seconds.* The identification of *P* during the progress of *A-V* rhythm is easy as a rule, after a careful comparison of the electrocardiograms with those of the preceding rhythm, for the beginning of the auricular complex lies before the initial deflection of the ventricle (Fig. 2).

When in a given experiment the change from *S-A* rhythm to *A-V* rhythm could be produced regularly and at will, the clamp was tightened and the desired grade of heart-block was induced. Curves were then taken of this heart-block and the change to *A-V* rhythm recorded in this phase of block. In Fig. 2 a control is seen. At the point marked by an asterisk *S-A* rhythm gives place, after a retardation of heart rate, to *A-V* rhythm, the *P-R* interval shortens from ·121 seconds to ·028 seconds. During the *A-V* rhythm a deflection resembling *Q* appears before *R*. This is in reality the beginning of an invert auricular complex. Fig. 3 shows a similar change of pacemaker in the same animal. 2 : 1 heart-block gives place to 1 : 1 heart-block with prolongation of the *P-R* interval soon after the application of cold. This change is the simple result of slowing of the natural pacemaker. But after three successive responses of the ventricle, the pacemaker changes, the *P-R* interval falling from ·211 to ·122 seconds. The new rhythm has the same starting point as in Fig. 2 but as a result of the bundle compression the

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* Comparator measurements.

P-R interval is wider (being ·122 seconds instead of ·028 seconds) ; it is in fact as wide as the normal P-R interval for this animal (·122 and ·121 seconds). The actual reduction of interval at the change of pacemaker is approximately the same in both figures (·093 and ·089 seconds, respectively). The partial heart-block lays bare the auricular complex corresponding to a beat of A-V nodal origin. Parallel changes are seen in Fig. 4 where A-V rhythm becomes established during a period of 2 : 1 block. With the change of pacemaker there is no change either in the direction of the block or in the degree of block : nevertheless the alternate auricular systole which yields a contraction of the ventricle lies nearer to the ventricular systole during A-V, as opposed to S-A, rhythm. The change is from ·165 to ·073 seconds ; the reduction is again approximately the same. It has been considered important to record transitions such as these, so that by a comparison of carefully measured intervals before and after the change, auricular contractions of A-V nodal origin might be identified with certainty. A comparison, too, of such curves as those shown in Fig. 2, 3 and 4, shows that the pacemaker has moved to the same focus in each instance. In each case the ectopic beats are represented by a complex which starts in the downward direction.

The auricular complex of A-V nodal rhythm may also be displayed fully and with surety, by a different procedure. If after the establishment of A-V rhythm the clamp is gradually tightened, or if a small amount of pressure is maintained (Fig. 5), synchronous contraction of auricle and ventricle is gradually lost : the P-R interval increases steadily until ventricular beats are dropped. An additional series of curves is published in Fig. 6, 7 and 8 : each series being from a distinct animal. Fig. 6 is the control, demonstrating the development of A-V rhythm at the application of cold. Fig. 7 shows the same change of pacemaker while partial heart-block prevails. At the beginning of the curve occasional ventricular responses are missed and the P-R interval varies according to the length of the preceding pause, as is usual. The same changes are seen during the progress of the A-V rhythm, though the P-R intervals are here shorter. If Fig. 6 and 7 are compared, it will be evident that the same ectopic pacemaker has established itself in each, though in Fig. 6 only the initial phases of the auricular deflections are visible. Fig. 8 is an example of the development of block, as a result of applying the clamp during A-V rhythm, in the same animal. The last illustration (Fig. 9) shows complete dissociation and auricular contractions of A-V nodal origin in a different animal.

Discussion.

The purpose of these experiments was twofold ; first, to ascertain the form of the auricular electric complex during A-V rhythm ; and second, to prove beyond dispute the origin of the A-V rhythm above the main division of the A-V bundle.

The shape of the auricular complex when the auricle and ventricle are beating synchronously in response to what is known as the A-V rhythm, is variable. As a general rule (eight out of nine experiments), the complex starts in a downward deflection ; often the whole complex consists of a depression upon which one or more minute secondary deflections are seen (Fig. 2 and 9). In other experiments the complex is polyphasic (Fig. 7 and 8) consisting of one or more small upward deflections and these being followed by a more or less conspicuous downward phase. In a number of instances these, the first and main deflections, are followed by a broad deflection, comparable to T in the ventricular complex (called by Hering Ta).

In electrocardiographic curves, which show the change from an S-A rhythm to an A-V rhythm, the type of ventricular complex is always maintained. The new focus, like the natural pacemaker, is responsible for supraventricular impulses. We may conclude from the shape of these ventricular curves that A-V rhythm arises above the main division of the bundle. This conclusion is fully confirmed by the present experiments, in which by pressing upon the main stem of the A-V bundle,* all the usual grades of block have been produced between auricle and ventricle ; the auricular rhythm remaining undisturbed. The seat of impulse formation was in each case at a higher level than the point of compression. The observations afford an additional evidence that synchronous action of auricle and ventricle is due to rhythmic discharges from the tissue termed the auriculo-ventricular node.

CONCLUSIONS.

1. When the auricle and ventricle beat synchronously or almost synchronously, as a result of cooling of the sino-auricular node, the new rhythm has its origin some distance above the division of the main stem of the auriculo-ventricular bundle. For compression of the bundle in these circumstances leads to auriculo-ventricular heart-block of forward type and in all its usual grades.

2. By producing forward heart-block the auricular complex, corresponding to A-V rhythm, may be dissociated from the ventricular, and its outline may then be studied. As a rule the main deflection is downwards in the electrocardiogram.

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* It has not been considered necessary to examine the heart histologically, the landmarks of the course of the bundle in the dog are so clear. The compression was applied midway between coronary sinus and the ventral edge of the septal segment of the tricuspid valve.

Fig. 2, 3, 4 and 5.   A series of electrocardiograms (lead *II*) from a single animal.   Fig. 2.
Control curve, showing *S-A* rhythm and its change to *A-V* rhythm upon applying cold to the
sulcus terminalis.   Fig. 3.   Showing the change from *S-A* rhythm to *A-V* rhythm with the
P-R interval originally prolonged.   Fig. 4.   Similar change during 2 : 1 heart-block.
Fig. 5.   Showing the effect of compressing the *A-V* bundle upon *A-V* rhythm ; the *P-R*
interval becomes prolonged and the ventricle fails to respond.   Abscissæ = ·2 seconds ;
ordinates = 10⁻⁴ volts.   The *P-R* intervals are expressed in seconds.

Fig. 6, 7 and 8.   A series of electrocardiograms (lead *II*) from a single animal.   Fig. 6.   Control
curve, showing the change from *S-A* rhythm to *A-V* rhythm upon applying cold.   Fig. 7.
The same change of pacemaker during partial heart-block.   Fig. 8.   The effect of
compressing the *A-V* bundle upon *A-V* rhythm.   Abscissæ, ordinates and intervals as above.

Fig. 9.   An electrocardiogram (lead *II*) from a dog, showing auricular contractions of *A-V*
nodal origin, and complete dissociation.
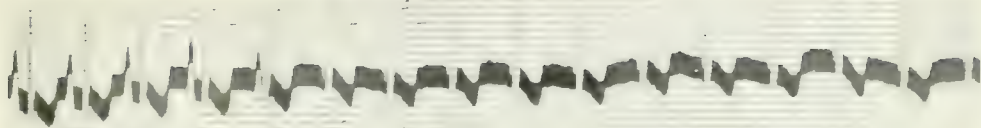
Fig. 2.

Fig. 3.

Fig. 4.
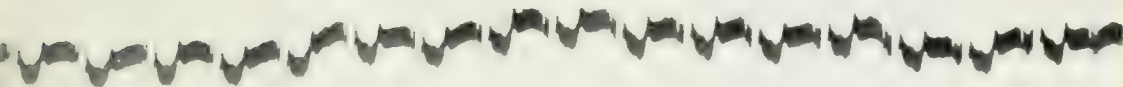
Fig. 5

THE SUSCEPTIBLE REGION IN A-V CONDUCTION.

By THOMAS LEWIS,* PAUL D. WHITE and JOHN MEAKINS.

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It has been established that auriculo-ventricular heart-block may be produced by direct interference with the main tract of muscular or neuro-muscular tissue which unites the auricles and the ventricles. When the bundle is cut or compressed and the ventricle then fails to respond in normal fashion to the auricular discharges, we see clearly cause and effect. According to our modern conceptions the path through which impulses spread from auricle to ventricle is damaged or broken, and the passage is prevented. In this form of experimental heart-block we have a perfect parallel to those clinical cases of heart-block in which circumscribed lesions are found in the same tract. Clinical heart-block of this form has a clear anatomical cause underlying it.

But there are forms of altered conduction, to use this term in its broadest sense, in which our knowledge is neither so sufficient nor so satisfying. Changes in conduction occur in a variety of circumstances ; both as a result of visible injury of the auriculo-ventricular bundle, and with more subtle influences. Thus the rate of conduction is changed physiologically in exercise and with altered heart rate ; it is changed from cycle to cycle when extrasystoles are forced from the auricle. Heart-block appears upon stimulation of the vagi. It is caused by the products of asphyxia and by a variety of poisons injected into the circulating blood.

Many questions of importance, both from the theoretical and practical standpoints, arise from these observations. At the present time we shall confine ourselves to one, and shall inquire if we have any knowledge pointing to the special susceptibility of a given region of the heart in respect of the conduction changes considered.

Evidently, a failure of the ventricle to respond to auricular impulses may be explained in a variety of ways ; the deficiency may lie in the auricle which fails to supply an adequate impulse ; it may be inherent in the junctional tissues and in any part of them ; it may be in the ventricles, it being supposed that they lack the power or intermediate means of response. Similar explanations may be applied, with certain qualifications, to simple retardation of conduction. Our inquiry is primarily one of localisation.

We possess certain preliminary evidences. From the morphological standpoint, the junctional tissues are first suspect ; for, as Gaskell states, those tissues which are most capable of rhythmic impulse formation are apparently slowest in conducting the contraction wave, and in the frog and tortoise the *A-V* ring is most susceptible ; here there is a natural line of block. It is to the homologues of this ring that we naturally turn in the first instance.

When we consider the mammalian heart our chief evidence lies in the character of the excitation process, portrayed by the galvanometer. The normal ventricular electrocardiogram, or ventricular complex, consists of a number of phases and, according to our present conceptions, the curve as a whole expresses an excitation process which starts and travels in a constant fashion. The normal complex is determined by the response of the ventricle to impulses which descend through well-defined channels ; it is the result of a supraventricular impulse, meaning by this term an impulse arising above the level of the main division of the auriculo-ventricular bundle.

Now it is the rule that in heart-block of vagal origin the ventricular complex remains unchanged in quality, though with the altered rate, it may be changed quantitively. It appears to us in the highest degree improbable that the ventricular complex could thus generally maintain its broad outline, if the susceptible region lay below the level of the chief bundle division ; for were the obstruction at a low level two or more points of depression and a simultaneous and equal depression of function in each would of necessity be postulated. The same argument may be applied to other forms of block ; *a fortiori* it may be applied to those in which complete block supervenes.

The maintenance* of the physiological ventricular complex in asphyxia, (complete heart-block) in adrenalin poisoning (complete),[2] in poisoning with strophanthine (partial), digitalis (partial and complete) (personal observations) and in anaphylaxis[5] (complete) is of significance to our minds and points to a region of the heart above the division of the bundle as the seat of the defect.

Observations.

Our observations were undertaken upon cats, fully anæsthetised with urethane and ether ; in all of the experiments the animals were decapitated, and the vagi were divided.

We were led to make the experiments described by previous experiments upon the effect of the vagus on *A-V* rhythm, already reported by one of us (this Journal, page 247) ; for it appeared from these experiments that the effect of vagal stimulation upon the sequence of chamber contraction is essentially different while *S-A* rhythm on the one hand, and *A-V* rhythm

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* We should say perhaps usual maintenance, for in some of the states cited, the normal form may be lost from time to time or experiment to experiment. But this fact does not detract from the force of our argument ; the alteration is attributable to a later and less constant effect on the branches of the junctional system.

on the other, predominates. When vagal impulses affect the heart beating in response to an *S-A* rhythm, the usual or *forward* type of heart-block is alone seen. When, on the other hand, an *A-V* rhythm is established, vagal stimulation produces reversed block, that is to say the auricle lags and may fail to respond, while the ventricle is apparently unaffected in this respect. It seemed from these observations that the chief seat of changed conduction lies, during vagal stimulation, in the *A-V* node and predominately to the auricular side of the impulse source. A separate series of experiments* upon extrasystoles carried out by two of us (Lewis and White) has led us to a similar conclusion in regard to the changes of conduction which occur as accompaniments of this form of cardiac disturbance. The view that the *A-V* node or immediately neighbouring tissue forms a susceptible point, so far as changes of conduction are concerned, appealed to us and we have sought and found strongly confirmatory evidence in the effects of asphyxia. Our procedure has been constant in each series of experiments. We produce changes in conduction by some form of interference and test the effect of dislocating the pacemaker from *S-A* to *A-V* node upon these changes of conduction. We anticipated that should the susceptible point be the same for vagal stimulation and for asphyxia we should obtain with the latter, not the ordinary effect of forward block, but reversed block. This anticipation has been fulfilled. The curves of asphyxia in cats need little description, they have been fully illustrated by Lewis and Mathison.[3] The curves of simple asphyxia in the present series were similar in every respect. After one or a few minutes of asphyxia, prolongation of the *P-R* interval is seen and is quickly complicated by missed ventricular responses; eventually auricular and ventricular rhythms become completely dissociated.

In producing *A-V* rhythm we have utilised cold applied to the sulcus terminalis and have taken repeated control curves during the course of an experiment, to ascertain the constancy of the reaction of the natural pacemaker to cooling. In these curves cooling is followed by slowing and by an abrupt change of mechanism, from the usual sequence to simultaneous beating in which the auricle slightly precedes the ventricle (Fig. 2*a*).

If, in the cat, *A-V* rhythm is established and maintained, the effects of asphyxia are as follows: In the initial stages of asphyxia the auricle usually beats immediately before the ventricle and the *P-R* interval is conspicuously curtailed. As asphyxia proceeds, the auricular and ventricular systoles become quite synchronous, so that *P* is lost in *R* (Fig. 2*b*, last cycle); after a little while *P* creeps out upon the far side of *R* and an *R-P* interval is developed (Fig. 3 and 1 *a, b, c*). This *R-P* interval gradually increases (Fig. 1 *a, b, c, 4 b*, and 5) and eventually the auricle fails constantly to respond. A condition is now established for a short while in which the auricle beats at exactly half the rate of the ventricle (Fig. 1 *d* and 5), and this condition may be identified readily by simple inspection of the heart. Finally and

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* Subsequently to be reported.

abruptly, all signs of auricular contractions disappear, both from the curves and upon inspection of the heart; yet at the change there is no alteration of ventricular rate.

We have also made a number of observations in which the origin of the impulses was changed at a given phase of heart-block. The transitions vary according to circumstance. Speaking generally they are as follows:

1. If the cold is applied before the development of a long *P-R* interval, then simple *A-V* rhythm becomes established (Fig. 2*a*), having the same time relations as in the controls.

2. If it is applied while the *P-R* interval is prolonged, then the action of auricle and ventricle becomes simultaneous, or *P* follows *R* (Fig. 4*a*).

3. If applied in the early stage of forward 2 : 1 block, then a long *R-P* interval is shown, but the auricle responds at each cycle.

4. If at a later stage, 2 : 1 reversed block is seen.

5. If applied during the final stage of complete dissociation, then the ventricular rate remains practically unaltered, but the auricle ceases to beat.

If, in simple asphyxia and after the development of a given grade of forward block, ventilation is re-established, generally speaking the heart recovers; it recovers gradually and shows the same grades of heart-block as during the induction stage, but in the reverse order. The same statement applies to the reversed block of asphyxia while the heart beats from the *A-V* node. Again, if the cold is withdrawn at any stage of an observation, the corresponding grade of forward block is quickly established. Thus, in Fig. 6, the first portion of the curve shows ventricular cycles only; the auricle has ceased to beat. The cold being withdrawn the normal auricular contractions return and complete dissociation is seen to be established.

Our chief observation is the contrast between the reaction of the heart to asphyxia when *S-A* rhythm and *A-V* rhythm prevail. In the first, forward heart-block develops; in the last, reversed block. The degrees of block in one or other circumstance are not very dissimilar; though it may be said that they are of a lesser order at a given time after the onset of asphyxia if *A-V* rhythm prevails. Thus 2 : 1 forward block gives place to a long *R-P* interval at the transition from one mechanism to the other in most instances. This is due in part at least to the relatively lower rates of impulse formation in the *A-V* node. The *S-A* node is depressed in the simple asphyxia at or almost at the time when block develops; the *A-V* node reacts to asphyxia in similar fashion.

The disappearance of the auricular responses to an *A-V* rhythm at a late stage of asphyxia is readily explained. It occurs at the stage of complete block, and the impulses fail to reach the auricle. The auricle is robbed of the *S-A* impulses by the application of ice-cold water to this node. It is guarded

from the *A-V* impulses by the block induced by asphyxia. Cut from its two chief sources of impulses it remains absolutely quiescent. It is necessary for us to state that our observations allow us to draw this last conclusion for the asphyxial state only. We know that both *S-A* and *A-V* rhythms are depressed by continued asphyxia, and it may be that hypothetical centres in other parts of the auricle might suffer similarly or in greater degree : so that although they do not become automatic in asphyxia when *S-A* and *A-V* nodes are thrown out of action. they might yield auricular responses under more normal conditions of nutrition.

Our observations in a measure affect the conclusions to be drawn from v. Ángyan's[1] observations. made some while since in this laboratory. v. Ángyan used the complete heart-block of asphyxia to test the effect of vagal stimulation upon the idioventricular rhythm. In the light of our present results. we now know that what has been termed idio-ventricular rhythm for the mammalian heart in the past, namely. the rhythm which governs the dissociated ventricle, may arise in the *A-V* node.* A rhythm of this kind springs from a different centre than that which develops automaticity when the *A-V* bundle is cut or compressed. When *A-V* rhythm is maintained and heart-block is developed as a result of asphyxiation the auricle alone shows abrupt changes of rate. The fall of rate in the ventricle is steady and progressive until after the establishment of complete block and at the time of its establishment shows no further alteration. The rhythm controlling the ventricle is propagated therefore from one centre throughout. The same statement applies to the ventricular rhythm when there is a change from *A-V* to *S-A* rhythm or vice versa. during the complete heart-block stage (Fig. 6). The *A-V* node controls the ventricle therefore in the complete heart-block of asphyxia. v. Ángyan's results are in reality the results of vagal stimulation upon *A-V* nodal impulses ; therefore. they are not strictly comparable to the similar observations of Hering and Erlanger who dealt with dissociation at a lower level of the heart.

In the late stage of simple asphyxia in cats. namely after the appearance of complete dissociation, the auricular contractions almost always disappear ; the change is abrupt and does not affect the rhythm or rate of ventricular contraction. When this happens the heart will not recover although re-oxygenated. The explanation of this phenomenon is not difficult. It is due to abrupt termination of the function of the *S-A* node. the *A-V* node continuing to control the ventricle. This change would account fully for the end curves of simple asphyxia in the cat and incidentally for certain of the curves of the dying human heart published by Robinson.[1]

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* It is probably as a result of a high level block that the greater rate of the ventricle in complete heart-block induced in the human subject by digitalis or its allies is due. We have attempted to test the level of block in strophanthine poisoning in cats. using repeated injections of 1 800 grain. But it has not been found possible owing to the extraordinary reaction of the *S-A* node to this drug. After the injections, and at a stage when heart-block was present. we have found repeatedly that cold has little or no effect on the *S-A* node.

Conclusions.

1.   While asphyxia produces a gradually increasing *forward* heart-block in the cat's heart beating from the S-A node, it produces a gradually increasing reversed heart-block when the heart chambers respond to the A-V node. From this we may conclude that in asphyxia the susceptible region in respect of changed conduction is the A-V node itself or tissues in its immediate vicinity.   The main defect is in a portion of the junctional system lying at a higher level (nearer the auricle) than the actual seat of impulse discharge in A-V rhythm.   This conclusion applies, in the cat, to rhythms in which the P-R interval is reduced to a small fraction of its original value.*

2.   Considering the results of the experiments here reported, and of similar experiments upon the effects of vagal stimulation and of extrasystoles† upon conduction in S-A and A-V rhythms, we are of opinion that the A-V node or tissue in its immediate vicinity is the most susceptible tissue in respect of changes in A-V conduction.

3.   In the cat, so asphyxiated that there is a complete functional break between A-V node and auricle, the application of cold to the S-A node brings about standstill of the whole of the auricular tissue.

4.   The effects of vagal stimulation in the automatic ventricle, as reported by v. Ángyan, are regarded as the effects of vagal stimulation upon the A-V rhythm, for in the complete block of asphyxia the dissociated ventricle is controlled by the A-V node.

5.   When at the end of a simple asphyxia of the cat the auricular contractions disappear abruptly during the stage of complete A-V dissociation, this change is attributable to depression of the pacemaker, the A-V node continuing to control the movements of the ventricle.

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[2]   Kahn.   Archiv. f. d. ges. Physiol., 1909, cxxix, 379.

    Lewis and Mathison.   Heart, 1910-11, ii, 47.

[3]   Robinson.   Journ. of exper. Med., 1912, xvi, 291 (Fig. 2).

    Robinson and Auer. Journ. of exper. Med., 1913, xviii, 548; (see also Auer and Robinson, *ibid*, xviii, 435 .

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* In the dog the level at which the impulses form appears to be variable.   In the cat, we have not seen slight reduction of the P-R interval, the reduction has always been conspicuous.

† Observations reported in an accompanying paper and in a paper to appear shortly.

Fig. 1c.
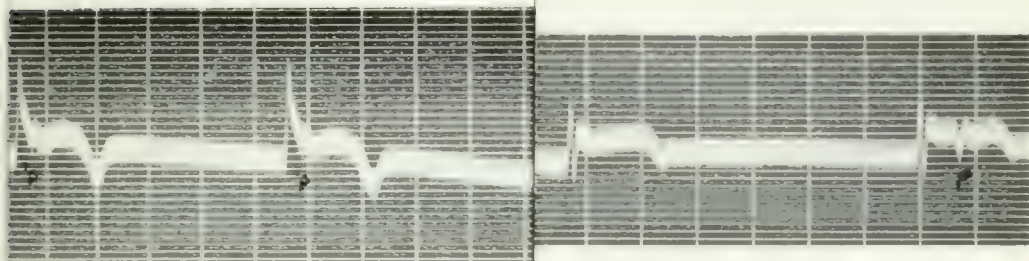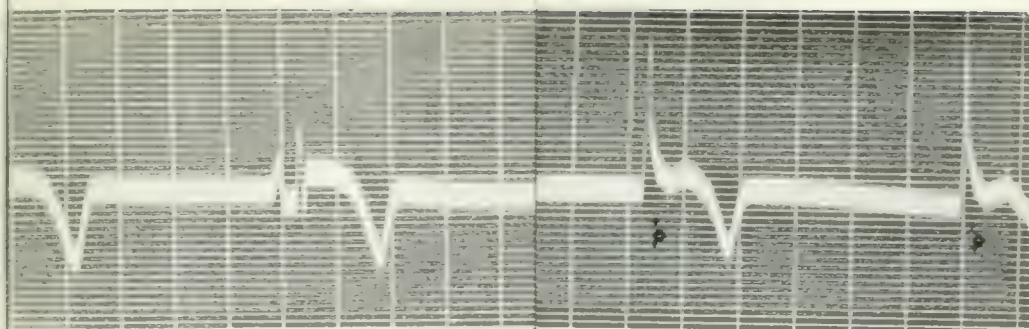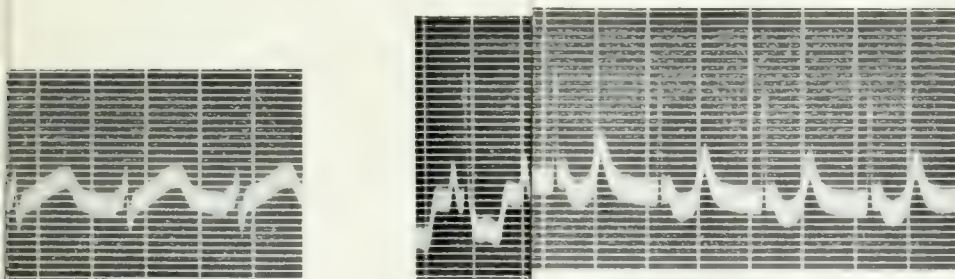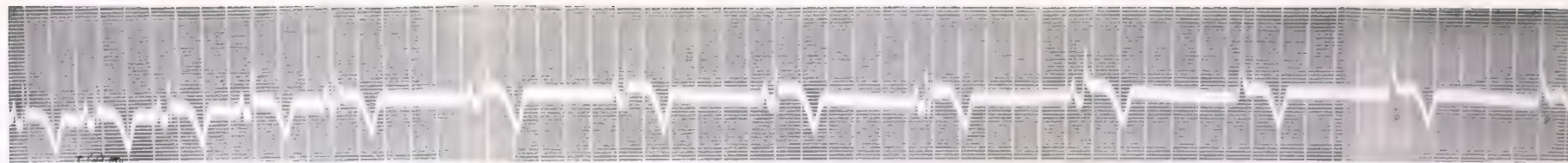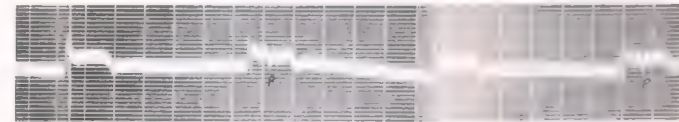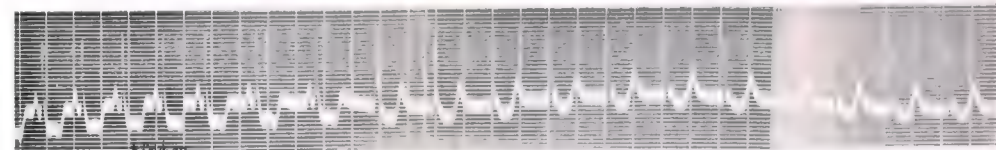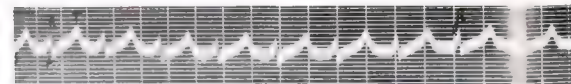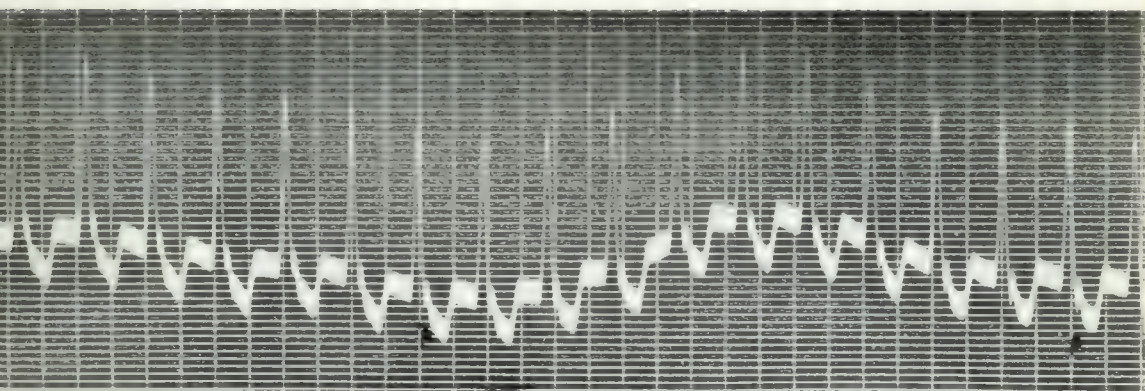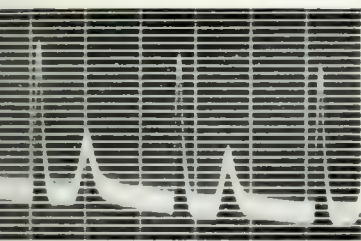
Fig. 5.
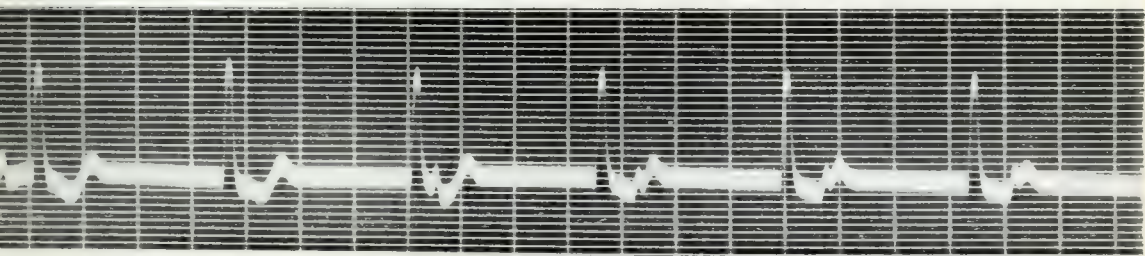
Fig. 6.
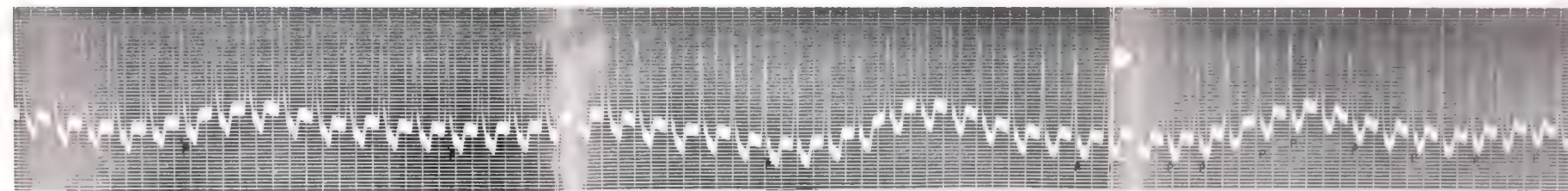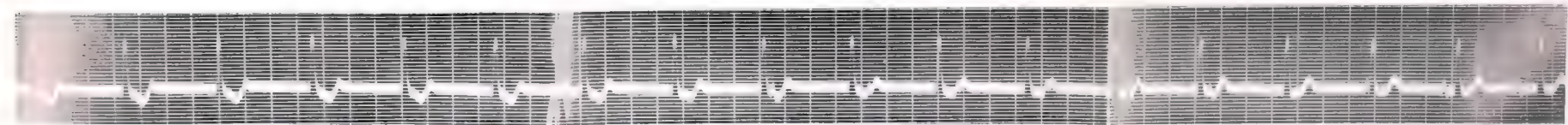
THE GENESIS OF VENTRICULAR EXTRASYSTOLES UNDER CHLOROFORM; WITH SPECIAL REFERENCE TO CONSECUTIVE VENTRICULAR FIBRILLATION.

By A. GOODMAN LEVY.

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Introduction and preliminary considerations.

THIS paper embodies an account of experiments originally undertaken to investigate a theory that was briefly suggested in a preliminary communication to the Physiological Society in January, 1911, namely, that ventricular fibrillation under chloroform was conditioned by an increase of intra-cardiac strain.

My conclusions as to the exciting causes of ventricular fibrillation under chloroform have already been communicated in this Journal,[11] and they do not embody the above mentioned theory, which has been abandoned, but the experiments relating to this branch of the investigation are now published as they present points of intrinsic interest and further tend to confirm my final conclusions as to the essential relation between cardiac stimulation and fibrillation of the chloroformed ventricles.

The general methods of experiment have already been sufficiently described in my former paper and need little further reference here. The whole of the work was again performed solely on cats. A damped mercurial manometer was again used in conjunction with the Hürtle in order to register the mean blood pressure changes.

In experiments under chloroform in which the peripheral resistance is raised the manometer does not afford such an accurate index of changes of peripheral resistance as it does when the animal is under the influence of some other anæsthetics, for under chloroform two forms of cardiac insufficiency may occur and complicate the record. In the first place, chloroform weakens the heart, which responds to an increase of peripheral resistance by dilating, so that the resulting rise of blood pressure is not proportional to the change in peripheral resistance, and secondly, the effect of the ventricular irregularities, which so frequently complicate the pressure curves, must be considered.

It is important to realise that when the heart is irregular it is not beating to the same mechanical advantage that it possesses when it is regular, and that consequently an irregular action of the heart involves a lowering of the vascular pressure, as I have frequently observed, and as Lewis[17] has shown to be the case in irregular acceleration of the heart. The reduction

of the blood pressure may or may not be made immediately evident in the
current pressure curve. In those cases in which the blood pressure is
unchanging at the moment of the incidence of irregularities a sudden fall
is indicated in the tracing (Fig. 1). When, however, the blood pressure is on
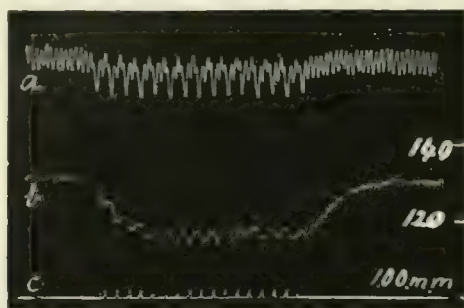
Fig. 1. Full size. Simultaneous Hürtle and damped mercurial manometer curves taken from
a carotid artery, showing a fall of blood pressure simultaneous with the onset of a trigeminal
heart beat (spontaneous).
   a.   Hürtle curve showing transition from regular to trigeminal beat.
   b.   Mercurial manometer curve recording mean blood pressure.
   c.   Horizontal line at 100 mm. Hg. pressure level.   Time marked in seconds.

the upward grade, then the occurrence of irregularities will affect the curve
according to the relative intensity of the central and peripheral changes, i.e.,
the resultant pressure curve indicates a fall, or remains stationary, or else
continues to rise but on a diminished grade. In those cases in which the
rise of pressure has been largely the outcome of an increased activity of the
heart, a very notable fall may occur if this organ is suddenly affected by
irregularities. These considerations are of importance in the interpretation
of the experimental curves, for the fall of vascular tension due to the occur-
rence of irregularities is not so much the result of a loss of energy on the
part of the ventricles as the outcome of the *misapplication of energy*, and when
the heart is passing from a regular into an irregular condition, then it is, I
think, evident that the blood pressure changes cannot be regarded as affording
a precise estimate of the variations in the stress under which the irregular
heart is acting.

SECTION I. THE PRODUCTION OF CHANGES OF BLOOD PRESSURE BY THE
INTRAVENOUS INJECTION OF DRUGS.

These experiments were devised with the idea of testing the presumed
relation between pressor vascular effects and ventricular fibrillation in
hearts lightly poisoned by chloroform. No doubt this theory is not tested
to best advantage by the injection of drugs, but these constitute one class of
pressor agents and have therefore to be considered. From an experimental
point of view they are valuable inasmuch as they are pressor agents which
can be applied with a minimum of operative manipulation, which, as has been
pointed out, appears to be of some importance. The method, however, is

obviously open to criticism because a foreign substance is introduced into the blood and this may or may not be known to exert some direct effect upon the heart's action : in fact, pharmacological knowledge is not always sufficiently exact to lead to decisive conclusions, and further some of this knowledge is based upon work which has been complicated by narcotic agents, which certainly in the case of chloroform, and possibly also in other cases, modify the reactions. I have therefore found it necessary in some instances to control the results obtained under chloroform by experiments under some other anæsthetic agent.

1. *The adrenalin group, which raises the blood pressure by stimulation of the sympathetic myoneural junctions in the arterioles.*

The action of adrenalin considered as one of cardiac stimulation has already been fully dealt with, and inasmuch as its cardiac action cannot be dissevered from its pressor action, it is difficult to assess the value of the latter property in relation to ventricular fibrillation. It is notable, however, that throughout a long series of experiments with adrenalin the onset of ventricular fibrillation has borne no relation to the height to which the blood pressure has been raised and the supposition of a causal relationship is thereby largely negatived.

It has elsewhere been briefly stated that ventricular fibrillation has not been observed as a result of the injection of adrenalin in an animal anæsthetised with *ether*, and some further remarks may now be appended in respect of the production of irregularities under such conditions. So far as my observations extend (six experiments) ordinary doses of adrenalin (0·032 to 0·065 mgms.) induce under ether a rise of blood pressure with a perfectly regular heart beat, but with large doses (0·26 mgms.) irregularities of a relatively low order of complexity may appear. These irregularities sometimes exhibit deviations from the chloroform type, but in the absence of electrocardiographic analysis, may be surmised to be allied in nature. I have embodied the results of consecutive injections into a single animal in Table I.

TABLE I.

The injection of adrenalin under ether.

Dose of adrenalin.	Degree of anæsthesia.	Initial.		Final.	
		Heart beat.	Blood pressure.	Heart beat.	Blood pressure
0·065 mgms.	Deep	Regular 180 per min.	136 mm.	Regular 220 per min.	174 mm.
0·065 mgms.	Lighter	Regular 160 per min.	130 mm.	Regular 180 per min.	164 mm.
0·260 mgms.	Light	Regular 140 per min.	144 mm.	Slightly irregular 120 (?) per min.	179 mm.

The heart when affected by ether and large doses of adrenalin is thus seen to be not entirely exempt from abnormal action, but that in its relative immunity from irregularity and its apparently absolute immunity from ventricular fibrillation it affords a remarkable contrast to its reaction to adrenalin under chloroform. This observation is important on account of the relative immunity of persons anæsthetised with ether from sudden death.

I have likewise tested the action of two other pressor amines, namely, epinine and tyramine,* both of which are related to adrenalin in chemical constitution and in pharmacological action : they are, however, less active, larger doses being required in order to obtain comparable results.

Epinine (di-hydroxphenylethylmethylamine). One mgm. was injected into the saphenous vein of a cat under 0·5% chloroform. A rise of pressure ensued, followed by death from ventricular fibrillation in a precisely similar fashion to that following the injection of adrenalin.

Tyramine (parahydroxyphenylethylamine). One experiment was likewise performed with this drug with an identical result.

2. *Nicotine, exerting a pressor effect through stimulation of the peripheral sympathetic ganglia.*

When a dose of from 5 to 10 mgms. of nicotine tartrate is injected into the saphenous vein of a cat lightly anæsthetised with chloroform the first effect is a fall of blood pressure accompanied by slowing of the heart beat which is attributed to an initial stimulation of vagal mechanisms ; this fall is followed by a rise of pressure accompanied by a multiple tachycardia which culminates in ventricular fibrillation (Fig. 2*a*). The results of three experiments are summarised in Table II.

TABLE II.

The action of nicotine under chloroform.

Number of experiment.	Dose.	Degree of anæsthesia.	Initial pressure.	Maximum pressure.	Result.
1	1st injection 10 mgms.	Well under 1·5%	110 mm.	148 mm.	Multiple tachycardia.
	2nd injection 10 mgms.	0·5%	132 mm.	170 mm.	V.F.
2	1st injection 10 mgms.	1·2% lightly anæsthetised	120 mm.	136 mm.	V.F.
3	1st injection 5 mgms.	1% lightly anæsthetised	106 mm.	122 mm.	V.F.

* I am much indebted to Dr. P. P. Laidlaw for sending me specimens of these and some other drugs mentioned in this paper.

Experiment 1 shows once again how full anæsthesia allows an irregular tachycardia alone to develop and protects the ventricles from fibrillation.

Nicotine, like adrenalin, is a cardiac stimulant as well as a vascular stimulant, for it excites the ganglionic cell stations of both cardiac and vasomotor sympathetic fibres, but it is in addition a cardiac stimulant in another sense, recent research (Cannon, Aub and Binger,[2] and more recently Dale and Laidlaw[7]) having shown that nicotine accelerates the secretion of the suprarenal glands. Therefore, in order to obtain the pressor action of nicotine alone, to the exclusion of its cardiac action, it is necessary to excise both the stellate ganglia and the suprarenal glands as a preliminary measure. Two experiments of this nature were performed and in both a similar result was obtained (Fig. 2*d*): with the rise of blood pressure the heart was somewhat accelerated and a few extrasystoles appeared, but the result was otherwise entirely dissimilar to that of the injection into the normal animal : the heart, however, was still fully irritable in that a subsequent injection of 0·065 mgms. of adrenalin readily caused it to fibrillate.

It is interesting to note that either of the above mentioned sources of cardiac stimulation acting alone is almost as effectual as both acting in unison, and this fact is illustrated in Fig. 2*b* and *c*, which illustrate the reaction to nicotine after excision of the suprarenals and stellate ganglia respectively.

The origin of the extrasystoles noted in Fig. 2*d* after excision of the stellate ganglia and suprarenals remains to be explained. It is not connected with the rise of blood pressure as this cannot be said to attain a height of sufficient magnitude. It has been presumed that nicotine possesses a direct stimulant action upon the cardiac muscle, but it is quite possible that the effect noted was an indirect adrenalin effect and that it does not exist after decapsulation. It is probable that the extrasystoles arise from the secretion, excited by the nicotine, of adrenalin from supernumerary bodies. And the existence of some unidentified source of cardiac stimulation is confirmed in several instances in the course of this paper.*

In six cats, anæsthetised by cerebral pithing in which the chloroform effect was thus excluded, a large rise of blood pressure was obtained on injecting nicotine : the heart beat was greatly accelerated in all, and remained regular in four ; in two cases a sequence of irregular beats was obtained, which soon, however, reverted to regularity. It would therefore appear that nicotine has *per se* some power of disturbing the heart's regular rhythm, but not to an extent approaching that obtaining under chloroform. This innate action of nicotine has not been further investigated.

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*Dale and Laidlaw[7] surmise the secretions of an unidentified adrenalin-like body as a result of nicotine injections.
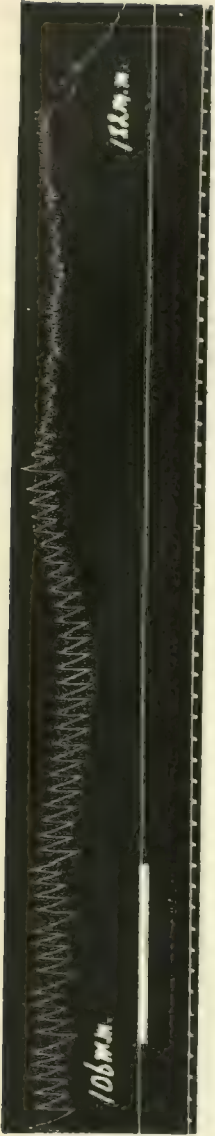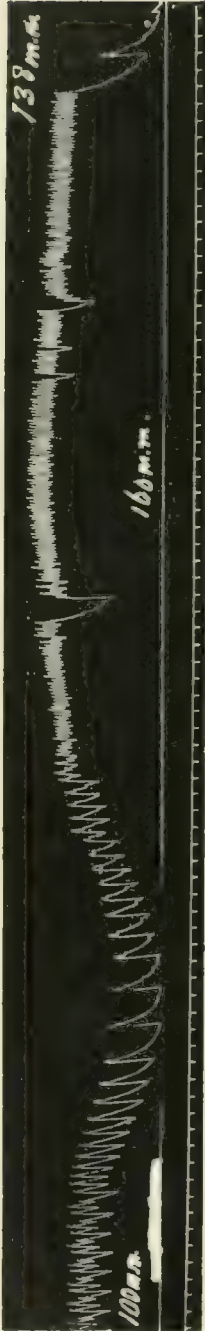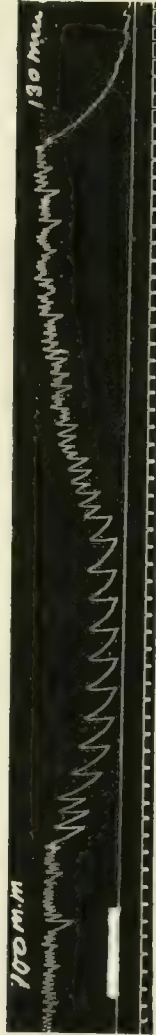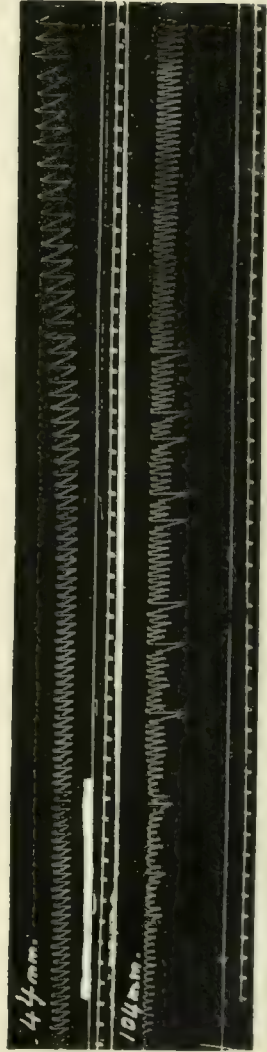
Fig. 2. × ¹₅. The effect of the intravenous injection of nicotine tartrate under light chloroform anæsthesia. Hürtle manometer. The signal line adjusted to the Hürtle abscissa. The signal marks the moment of injection. Time marked in seconds.

a. Normal reaction to 5 mgms. of nicotine tartrate in an intact animal under 1% CHCL₃. Before injection every fifth beat is an extrasystole. First stage, fall of blood pressure with a slightly retarded and regular beat. Second stage, rise of blood pressure with onset of multiple tachycardia. Third stage, ventricular fibrillation, with fall of blood pressure.

b. Reaction of 10 mgms. nicotine tartrate in a cat under 1% CHCL₃ with both suprarenals extirpated. Before injection, every third beat is an extrasystole. First stage, marked retardation of beat with fall of blood pressure. The second stage is broken by short periods of ventricular fibrillation. Third stage permanent ventricular fibrillation.

c. Reaction of 10 mgms. nicotine tartrate in a cat under 0·5% CHCL₃ with both stellate ganglia excised. Before injection a multiple tachycardia is exhibited. Stages as in (*a*).

d. Reaction of 10 mgms. nicotine tartrate in a cat under 0·8% CHCL₃ with both stellate ganglia and both suprarenal bodies excised. Before injection, the heart beat is regular. First stage, retarded heart beat with rise of blood pressure. Second stage, occasional extrasystoles and heart beat accelerated slightly above the normal. Third stage, fall of blood pressure with regular beat ; the pressure eventually falls to its initial level. A piece of the curve has been cut out between the two strips shown ; this shows precisely similar features.

(a)

(b)

(c)

(d)
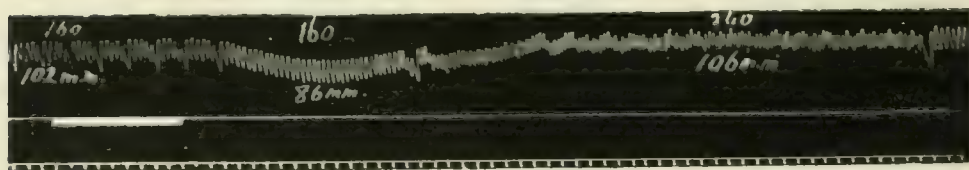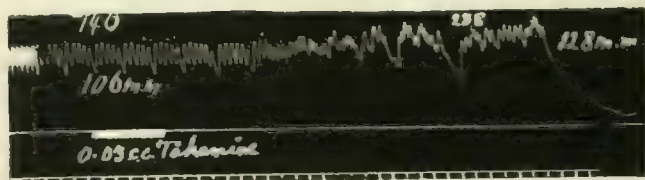
Fig. 3. × ½. The injection of pituitary extract under light chloroform anæsthesia. Hürtle manometer. The figures above the curves represent rates of heart beat ; the figures below the curves represent blood pressures in mm. Hg. The signal line is adjusted to the Hürtle abscissa. Time marked in seconds.

    a. Usual type of action. Firstly a fall of blood pressure with acceleration of the heart beat, secondly a rise of blood pressure with retardation of the beat. The heart beat remains regular throughout. 0·6 c.c. pituitary extract. 0·7 % chloroform.

    b. Onset of irregularities with the fall of pressure. The irregularities disappear as the blood pressure rises and the heart beat is retarded. Pituitary extract 0·6 c.c.. Chloroform 1 %.

    c. A multiple tachycardia arising in the second stage ; after a brief duration the beat suddenly reverts to a regular type. At the time of injection every fifth beat was an extrasystole. Pituitary extract 0·9 c.c.. Chloroform 0·5 %.

    d. The injection of 0·03 mgms. adrenalin following the experiment *c.* The ventricles are perfectly sensitive and fibrillate, showing that the different result of the preceding pituitary reaction was not due to adverse cardiac conditions. Chloroform 0·5 %. Previous to injection every fifth beat was an extrasystole.

In concluding my remarks upon the action of nicotine under chloroform it must be pointed out that the experiments do not absolutely preclude the production of ventricular fibrillation by a pure pressor effect, for the pressor

action in those experiments in which the cardiac stimulant action was excluded was not an intense one, or at least the maximum pressure reached was not at a high level (104 mm.). Nevertheless the results are in complete agreement with my conclusions that ventricular fibrillation under chloroform is a result of cardiac stimulation and that it does not occur in the absence of some such stimulation.

3. *Drugs exerting a vasoconstrictor effect by direct action upon the unstriated muscle of the vessels.*

Extract of pituitary gland. This drug was administered by intravenous injection. A $10^0/_0$ extract was employed in doses of from 0·3 to 1·2 c.c. and diluted with an equal bulk of normal saline. The action appeared to be identical in the case of each of the two commercial preparations employed.

TABLE III.

The intravenous injection of pituitary extract under chloroform anaesthesia.

The dose denotes quantities of a 10% extract.

Experiment.	Chloroform.	Dose.	Sequence of injection.	Blood pressure changes.	Pulse rate.	Remarks.
1	$0·8^0/_0$	0·4 c.c.	i	106 mm.	170	Regular.
				98	180	,,
				118	150	,,
	$0·5^0/_0$	0·7 c.c.	ii	106 mm.	140	,,
				92	160	,,
				114	120	,,
2 (Fig. 3*a*)	$0·7^0/_0$	0·6 c.c.	i	89 mm.	160	Regular.
				76	170	,,
				106	140	,,
	$0·5^0/_0$	1·2 c.c.	ii	104 mm.	160	,,
				87	160	,,
				114	140	,,
3	$0·8^0/_0$	0·2 c.c.	i	72 mm.	120	Regular.
				96	120	,,
4	$1·5^0/_0$	0·6 c.c.	i	90 mm.	100	Regular.
				75	120	,,
				90	140	3 extrasystoles.
				104	70	Bigeminal beat.
				112	116	Regular.
5	$1^0/_0$	0·2 c.c.	i	84 mm.	160	Regular.
				82	180	,,
6 (Fig. 3*b*)	$1^0/_0$	0·6 c.c.	i	101 mm.	150	Regular
				65	180	,,
					220	Irregular.
					130	Regular.
				120	110	,,
(Fig. 3*c*)	$0·5^0/_0$	0·9 c.c.	ii	102 mm.	160	Extrasystole every fifth beat.
				86	160	Regular.
				106	240	Multiple tachycardia.
7	$1^0/_0$	0·2 c.c.	i	87 mm.	100	Trigeminal beat.
				82	100	Occasional extrasystoles.
				86	240	Multiple tachycardia.
				106	300	,, ,,

In the above table a series of seven experiments is summarised, and of these, experiments 2 and 6 are illustrated in Fig. 3. It is seen that the initial result of the injection, with one exceptional case, was a depression of blood pressure.* With this fall the heart rate was accelerated in all cases in which the beat was regular.† The pressor effect is secondary and it is apparent that this, in the presence of chloroform is not very great, the largest rise of blood pressure observed being 28 mm., the average rise being 16·1 mm. only. With the rise of pressure, there is generally a retardation of the beat provided the heart remains regular.

In three cats the heart remained regular throughout the experiment and in the remaining four cats irregularities were produced, which, in three instances, attained the complexity of a multiple tachycardia, but it is a notable fact that these irregularities were not conditioned by a rise of blood pressure ; in fact they appeared in conjunction with a negligible rise, or at any point in the pressure curves, even at the lowest point of the primary fall (Fig. 3 _b_ and _c_). In no case did ventricular fibrillation occur as a result of the injection.

It is thus evident that pituitary extract possesses an uncertain power of exciting irregularities under chloroform, but a power in no degree comparable to that possessed by adrenalin. In Fig. 3_d_ this fact is illustrated by the control injection of 0·03 mgms. of adrenalin, and it is seen that the heart is still irritable and reacts by fibrillating in the usual fashion.

The incidence of ventricular irregularities is therefore not in this case determined by the rise of blood pressure, and it remains to consider the interpretation of their cause. Ott and Scott[21] hold that pituitary extract stimulates the suprarenal bodies to increased activity ; pituitary extract has further a distinct stimulating effect upon the force of the beat ; Dale[6] has shown that this stimulant action is evinced on perfusing the coronary arteries with the extract, and it is thus independent of adventitious aid from the suprarenals. To one or other of these causes acting in varying degree the incidence of these irregularities may be ascribed.

Apart from theoretical considerations the experiments have an important clinical application, for pituitary extract has been largely employed to counteract shock in operations under chloroform. This drug possibly cannot be regarded as an absolutely safe agent for such a purpose, but in comparison with adrenalin employed for the same purpose it is relatively innocuous.

Barium chloride. This is a powerful vasoconstrictor agent and very readily induces ventricular fibrillation in the lightly chloroformed heart.

The drug was injected into both the arterial and venous circulation in a $\frac{N}{1}$ solution, in doses of from 0.75 c.c. to 2 c.c. (15 to 40 mgms.).

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* Oliver and Schäfer observed a depression of pressure on the _repetition_ of a dose only ; in my experiments under chloroform it has been the rule as the result of the _initial_ dose.
† This acceleration was seen also in a cat in which the suprarenals had been excised.

The relation of this drug to ventricular irregularities and fibrillation is complicated and it is therefore not possible to draw any conclusions in connection with its pressor action considered alone. In the first place $BaCl_2$ strengthens the heart beat, and thus a stimulant factor is presented. Secondly the effect of $BaCl_2$ upon the secretion of adrenalin, if any, remains to be investigated. Moreover $BaCl_2$ is a cardiac poison of a peculiar nature, for it is held to have the power of initiating ventricular irregularities and fibrillation apart from the presence of chloroform, and, when given in small doses, to act in a similar manner to chloroform in that it predisposes the heart to exhibit ventricular irregularities from appropriate stimuli, as for instance by the action of adrenalin or by stimulation of an accelerator nerve (Rothberger and Winterberg[22]), or on section of the vagus trunks (Cushny and Edmunds[5]). In my own experience $BaCl_2$ certainly differs from the other pressor agents I have investigated in that it may produce ventricular fibrillation in a cat under ether : this happened in two of three cats in which an intravenous injection was made under ether, the ventricles rapidly passing into fibrillation. In order to ascertain the action of $BaCl_2$ in animals not under any general anæsthetic at the moment of injection, I performed five experiments upon cats in which the brain had been pithed : the heart remained apparently regular in four experiments, but in one an irregular tachycardia of 10 seconds duration appeared after an injection of 40 mgms.

Further investigation thus appears to be necessary for a full explanation of the action of $BaCl_2$, and it is obviously at present useless for the elucidation of the blood pressure question under consideration.

4. *Drugs exerting a pressor effect through stimulation of central nervous mechanisms.*

Glycolic acid. This drug stimulates the vaso-constrictor centres powerfully and, like lactic acid, at the same time dilates the heart and the blood vessels through a direct action on the muscle fibres. Its actions are thus complex and antagonistic, but Mathison[19] has shown how they may be analysed in accordance with the route of injection ; when the injection is made into the jugular vein the initial effect is a fall of blood pressure due to cardiac depression, and this is followed by a rise of pressure, but when the injection is made into a carotid artery the pressor effect is manifested at once. I find that in cats under chloroform a considerable and fairly rapid rise of pressure is caused by injecting 20 to 80 mgms. into a carotid artery. The cannula connected with the manometer was inserted into the crural artery in these experiments in order to avoid ligature of both carotid arteries, a procedure which is liable to introduce complications. Briefly stated, the action of glycolic acid thus injected under chloroform is to initiate an irregular tachycardia, sometimes of a very rapid type (*e.g.*, 390 beats per minute) but this never passes into ventricular fibrillation (Fig. 4). Furthermore the subsequent intravenous injection of adrenalin does not produce ventricular
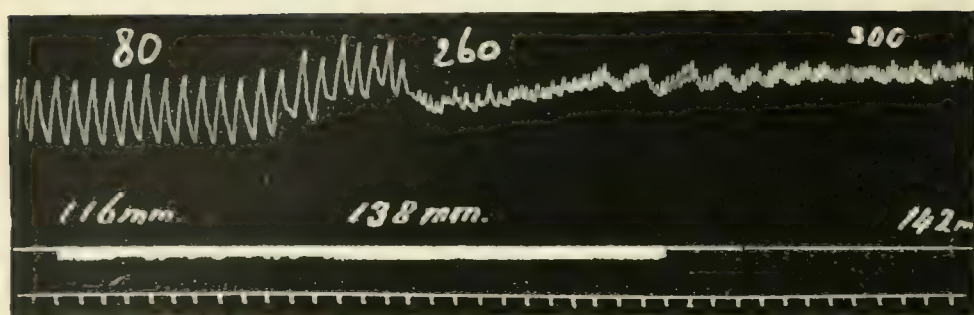
Fig. 4. Full size. Injection of 5 c.c. glycolic acid solution into a carotid artery under 1·1°/₀ CHCL₃. The blood pressure rises and the heart passes from a regular beat into a rapid irregular tachycardia. The blood pressure finally rises to a height of 162 mm., Hürtle manometer. The upper row of numbers indicates rates of heart beat, the lower row blood pressures. The signal mark indicates the time of injection and is on the abscissa line. Time in seconds.

fibrillation even when fourteen times the ordinarily effective dose is injected. Glycolic acid thus protects the ventricles against fibrillation. (Table IV.)

TABLE IV.

The intracarotid injection of glycolic acid.

Experiment.	CHCL₃.	Dose.	Blood pressure.		Control.	Remarks.
			Initial.	Final.		
1	1°/₀	76 mgms.	142 mm.	196 mm.	Adrenalin 0·12 mgms.	No V.F. from either re-agent.
2	?	38 mgms.	108 mm.	145 mm.		.. .. ..
3	1°/₀	38 mgms.	150 mm.	194 mm.	Adrenalin 0·12 mgms.	.. .. ..
4	0·8°/₀	19 mgms.	118 mm.	166 mm.	Tyramine 2 mgms.	. .. ..
5	0·5°/₀	76 mgms.	160 mm.	234 mm.		.. .. .. Previous to injection the abdominal aorta had been ligatured.
6	0·8°/₀	45 mgms.	140 mm.	206 mm.	Adrenalin 0·06 mgms.	No V.F. from either re-agent. Previous to injection both vagi had been cut.
7	1·1°/₀	76 mgms.	116 mm.	162 mm.	Adrenalin 0·42 mgms.	No V.F. from either re-agent.

This protective effect of glycolic acid against ventricular fibrillation is connected with its cardiac action and not with its central nervous action; this fact may be demonstrated by making the injection slowly into a vein at a distance from the heart, such as the saphenous vein; under such circumstances and even under a low percentage of chloroform no rise of blood pressure may result and the heart's rhythm may be very little disturbed, showing that there has been little or no central nervous effect, but a subsequent injection of adrenalin demonstrates that the acid has acted upon

the heart protecting it from fibrillation. This protection is abolished by injecting an equivalent quantity of sodium hydrate and the heart then becomes once more highly irritable and fibrillates when stimulated by adrenalin. The following experiment illustrates this point :—

Experiment, April the 25th, 1911. *Cat.* 0·5% chloroform. All injections made into saphenous vein.
  i.   2·5 c.c. } (38 mgms.). Glycolic acid injected. No rise of blood pressure and no tachycardia.
  ii. 0·12 mgms. adrenalin injected. Tachycardia, but no ventricular fibrillation.
  iii. 2·5 c.c. $\frac{N}{2}$ NaHo injected.
  iv. 0·12 mgms. adrenalin injected. Permanent ventricular fibrillation ensues.
  This experiment has been repeated and confirmed.

The depressing action of glycolic acid upon the heart is well shown when it is injected into a jugular vein under chloroform ; it then reaches the heart in a relatively undiluted condition and a marked fall of blood results. Under such circumstances. if the heart be previously exhibiting an irregular action. the irregularities tend to disappear, as they did in two experiments out of three of this nature. (Fig. 5.)
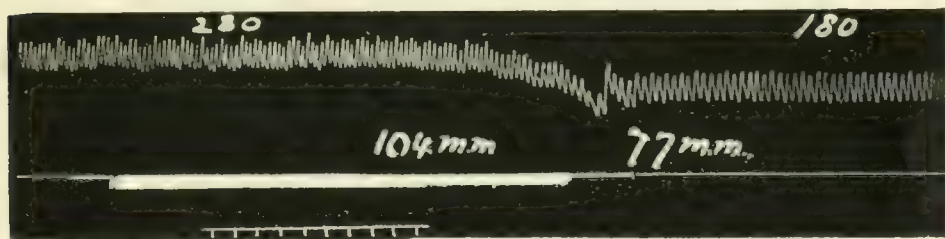
Fig. 5. Full size. Injection of 5 c.c. $\frac{N}{2}$ glycolic acid solution into the right jugular vein under 1% CHCL₃. The blood pressure falls and the heart passes from a rapid irregular beat to a regular slower rhythm. Hürtle manometer. The upper row of numbers indicates rates of heart beat, the lower row blood pressures. Signal mark indicates the moment of injection and is on the Hürtle abscissa line. Time in seconds.

The cardiac action of glycolic acid is thus comparable to that of the higher percentages of chloroform. In neither case is the onset of cardiac irregularities prevented when the heart is powerfully stimulated. but in both cases the ventricles are prevented from fibrillating ; and in both cases there is a tendency to restrain pre-existing irregularities and make the beat regular.* The action of glycolic acid thus tends to substantiate the view I have already advanced that full doses of chloroform prevent ventricular fibrillation through its power of depressing and dilating the heart : glycolic acid is likewise a cardiac depressant and dilating agent and has a like effect.

These experiments do not exclude a relation between pressor effects and ventricular fibrillation. but they further confirm the far greater importance of cardiac conditions in relation to this event.

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* The reservation must be made that the change in beat may in this case be conditioned by the fall in blood pressure. (Page 321.)

Strychnine. The intravenous injection of strychnine is generally
followed by a great rise of blood pressure, which may attain a height of
200mm. or more.   This pressor effect is of complex origin (Cushny[1]) ; it is in
part due to a vasoconstriction in the splanchnic area from stimulation of
spinal centres, and in part the result of muscular convulsions, and this
muscular, that is to say mechanical, cause is the main factor in the rise of
pressure under chloroform ; so, at least, I judge from experiments in which
the muscular convulsions were excluded by means of curari.

It is further stated that the heart is accelerated both during and after
the termination of the convulsions.   It may safely be surmised that the
cardiac accelerators and the secretory nerves of the suprarenal bodies, forming
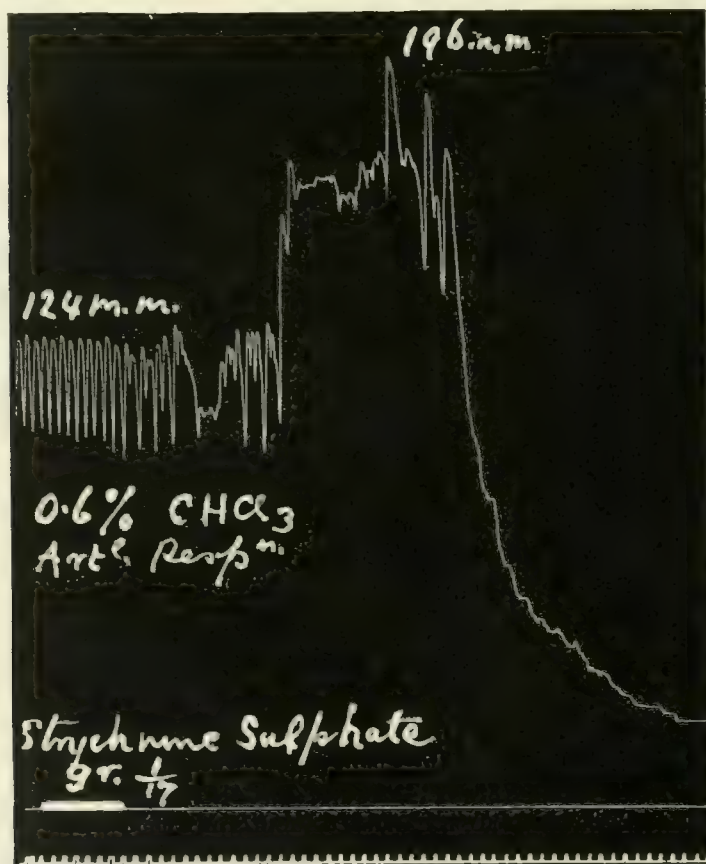
Fig. 6.   × ⅝.   Intravenous injection of 4 mgms. of strychnine sulphate under 0·6% CHCL₃
With the onset of convulsions the blood pressure rises to 196 mm., the heart beat becomes
irregular and rapid and indecipherable in the curve, and the tracing terminates in a fall of
blood pressure due to ventricular fibrillation.   Mercurial manometer.   Artificial respiration.
The signal mark denotes the moment of injection.   The signal line adjusted to manometer
abscissa.   Time in seconds.

part of the sympathetic system, are stimulated in conjunction with the vaso-constrictor nerves as a result of an unselective convulsive nervous output, and that the cardiac acceleration is thus, at least in part, accounted for.

Under light chloroform anæsthesia ventricular tachycardias are the invariable sequence, and ventricular fibrillation the occasional sequence only, of an intravenous injection of strychnine salts (Fig. 6). Ventricular fibrillation would appear to be favoured by a percentage of chloroform which is not too low ; thus with 1% vapour I obtained two instances of ventricular fibrillation in a series of four experiments, which is a higher proportion than ordinary. On the other hand in three experiments under 2% chloroform the heart showed little tendency to become completely irregular.

Table V comprises a separate series of six experiments under low percentages of chloroform, two of which resulted in ventricular fibrillation.*

<div align="center">TABLE V.</div>

The intravenous injection of strychnine sulphate under light chloroform anæsthesia.

In this series artificial respiration was employed in all cases to exclude the effect of asphyxia from respiratory spasm, but in animals breathing naturally the results are little, if at all, modified.

Experi- ment.	CHCl₃.	Dose.	Blood pressure.		Remarks.
			Initial.	Final.	
1	0.5%	3·8 mgms.	150 mm.	212 mm.	No V.F.
2	0.8%	4·6 ,,	106 ,,	148 ,,	No V.F.
3	0.6%	3·8 ,,	124 ,,	196 ,,	V.F.
4	0.8%	3·8 ,,	96 ,,	206 ,,	No V.F.
5	?	3·2 ,,	86 ,,	174 ,,	No V.F. Vagi previously cut.
6	0.8%	4·6 ,,	120 ,,	173 ,,	V.F.

Average rise of blood pressure in fibrillation cases = 62·5 mm.; in non-fibrillation cases = 75·5 mm. Average maximum blood pressure in fibrillation cases = 184·5 mm. ; in non-fibrillation cases = 185 mm.

If the cardiac accelerator nerves be cut, or the stellate ganglia be excised previously to the injection of strychnine, then the reaction is notably modified. In Table VI it will be seen that in six experiments of this kind no instance of ventricular fibrillation was observed although a powerful pressor effect was generally obtained. Further in two of these experiments alone did I obtain brief periods of a rapid tachycardia ; otherwise the irregularities were of a markedly modified type and occurred in a slow succession only.

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* Many animals, especially those more deeply anæsthetised, succumb after the convulsions. The blood pressure in these cases falls gradually, and not precipitately as in ventricular fibrillation. Respiratory and general exhaustion no doubt play a part in such instances of death.

TABLE VI.

The injection of strychnine sulphate into cats under chloroform deprived of their cardiac sympathetic innervation.

Experi-ment	CHCL	Dose.	Blood pressure.		Remarks.
			Initial.	Maximum.	
1	1%	4·6 mgms.	77 mm.	184 mm.	No V.F.
2	1%	5·0 „	100 „	180 „	..
3	0·5%	5·4 ..	50 „	160 „	..
4	1%	4·3 ..	142 „	226 ..	..
5	1%	4·0 „	108 ..	114 „	..
6	0·5%	5·0 ..	52 .,	152 ..	..

Average rise of blood pressure = 81 mm.
Average maximum blood pressure = 169 mm.

In three cats excision of both suprarenals and stellate ganglia was performed and then strychnine injected under chloroform. In two instances the heart was slightly accelerated but remained perfectly regular ; a tracing of one of these experiments is shown in Fig. 7 : the rise of blood pressure was large = 57 mm., yet the pulse tracing remained remarkably regular.
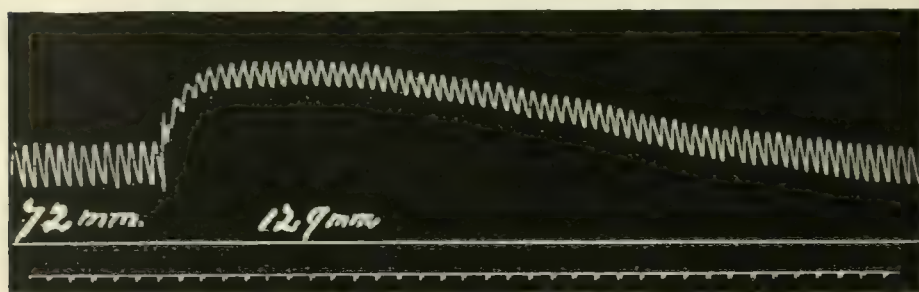
Fig. 7. Full size. Intravenous injection of 4 mgms. of strychnine sulphate under 0·5% chloroform into a cat in which both suprarenal bodies and both stellate ganglia had been excised. The blood pressure rises with the onset of convulsions but the heart beat remains perfectly regular though slightly accelerated. Hürtle manometer. Time in seconds.

In the third cat a period of irregularities (180 beats per minute) of twelve seconds duration was observed, at a blood pressure of 122 mm. Hg. ; these irregularities may be accounted for as the result of adrenalin excretion from supernumerary suprarenal bodies, as in the similar experience with nicotine.

The conclusion may be drawn from these experiments that the occurrence of ventricular fibrillation is not conditioned by a rise of blood pressure alone. In Table V it is seen that ventricular fibrillation is not conditioned by the

highest maximum blood pressures or by the greatest rise of blood pressure, and Table VI shows that in the absence of the stellate ganglia it does not occur at all, although the rise of pressure be great. When all known paths of cardiac stimulation are excluded (excision of stellate ganglia and suprarenals) the rise of blood pressure may be retained with a regular heart beat. The conclusion appears irresistible that the rise of blood pressure as a result of strychnine injections, being mainly mechanical, does not condition ventricular fibrillation. Ventricular fibrillation is conditioned by the central nervous effects of the strychnine which are of variable intensity, and therefore its occurrence is variable.

5. Drugs which exert a vaso-dilator action.

Apocodeine. This drug causes vaso-dilation by paralysing the sympathetic ganglia (Dixon[8]). It has a cardiac action, which is exerted on
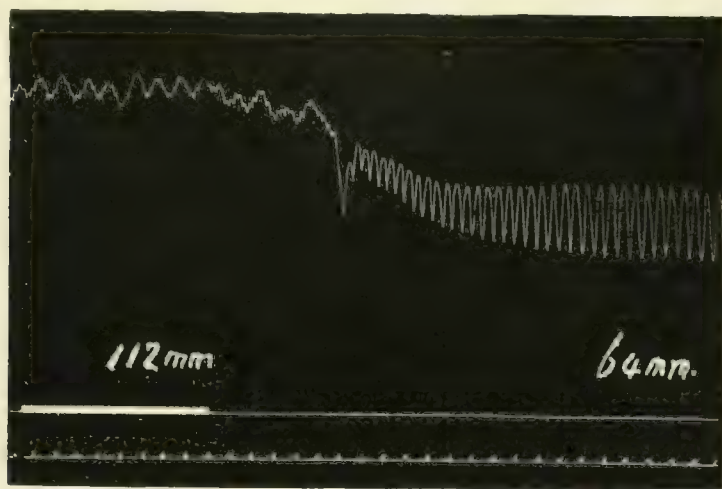
Fig. 8. × ½. The intravenous injection of 10 mgms. of apocodeine into a cat under 1·0 % chloroform. The blood pressure falls and the heart passes from an irregular tachycardial condition to a regular beat. The signal line is adjusted to the manometer abscissa. Mercurial manometer. The figures represent mean blood pressure. Time in seconds.

the cardiac nerve endings ; this complex and apparently varies with the dose employed, but it may be inferred that in the experiments described below, the resultant cardiac effect is not one of depression. Two experiments were performed :—

Experiment I. 10 mgms. of apocodeine were injected into the saphenous vein of a cat under chloroform, the heart exhibiting a typical irregular tachycardia of 300 beats per minute (Fig. 8). As a result the blood pressure fell from 112 mm. to a mean pressure of 64 mm., the heart becoming quite regular with a beat of 120 per minute.

Experiment II. 7 mgms. apocodeine injected into the saphenous vein of a cat under 1 % chloroform. The vagi had been previously cut. The blood pressure fell from 126 mm. to 72 mm. and heart beat changed gradually from a rapid and very irregular tachycardia to a regular beat of 270 per minute. A previous injection of 2 mgms. had caused a fall from 152 mm. to 112 mm., and the irregularities were not entirely abolished.

An indication is afforded by these experiments that a fall of pressure may result in the disappearance of irregularities under chloroform, an indication which is confirmed in a later section in which the significance of the reaction is discussed (page 321).
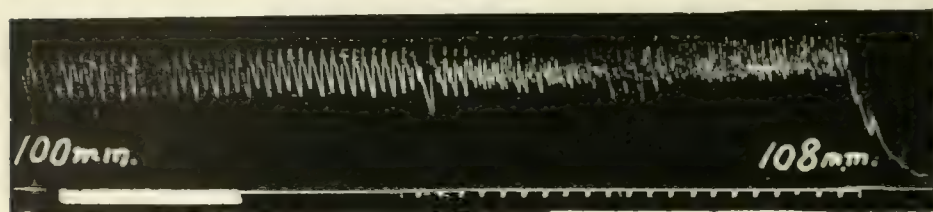
Fig. 9. Full size. The intravenous injection of 10 mgms. of tetrahydropapaveroleine hydrochloride under 0·8% chloroform. There is a slight rise of blood pressure only and the ventricles pass from a regular beat to an irregular tachycardia and finally fibrillate. Hürtle manometer. Time in seconds.

Tetrahydropapaveroleine. This drug causes a vaso-dilation by direct action upon the plain muscles of the arterioles, and it provides an interesting contrast to apocodeine in that it is at the same time a powerful cardiac stimulant, both in relation to the rate and force of the beat (Laidlaw[12]). The results of four experiments are shown in Table VII.

TABLE VII.

The intravenous injection of tetrahydropapaveroleine chloride.

Experiment.	Chloroform.	Dose.	Time in Seconds.	Blood pressure.	Character of Heart Beat.
1	0·5%	5 mgms.	0 45 120	72 mm. 96 ,, 136 ,,	Regular. Irregular. V.F.
2	1%	6 mgms.	0 26 60	100 mm. 76 ,, 90 ,,	Irregular. Regular. V.F. following irregularity.
3	2%	10 mgms.	0 10 40	128 mm. 104 ,, 120 ,,	Irregular. Regular. Momentary V.F. following irregularity.
4 (Fig. 9)	0·8%	10 mgms.	0 8 29	100 mm. 108 ,,	Regular. Irregular. V.F.

Under chloroform the depressor effect of this drug is neither marked nor constant ; however, a fall was noticed in two experiments and this fall was accompanied by a temporary disappearance of pre-existing irregularities as in the case of apocodeine. This fall of pressure is an early effect, and later the pressure wholly or partially recovers or may even rise considerably as a result of the augmented cardiac action, but the ventricles are caused to pass into

fibrillation whether the blood pressure has risen above its initial height or not ; they may in fact fibrillate permanently at a slightly lowered pressure. Fig. 9 demonstrates how this drug reacts on the chloroformed heart in a way similar to that of adrenalin in the absence of the pressor effect of the latter, the blood pressure rising in this instance 8 mm. only.
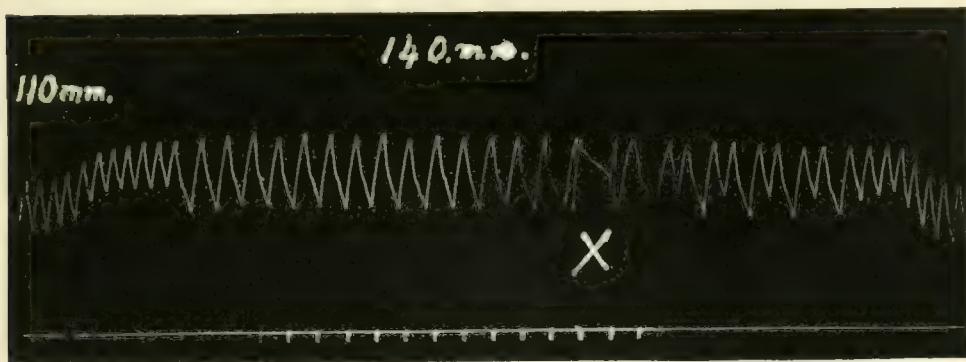
Fig. 10. Compression of the abdominal aorta under 0·6% chloroform. Initial heart beat regular, on compression the blood pressure rises from 110 mm. to 140 mm. and the beat becomes at first bigeminal and later trigeminal. The premature beats are not well transmitted and are indicated by the length of pause between the beats. On removing the compression the beat resumes its original character. At **X** there was a temporary irregular movement of the kymograph. Hürtle manometer. Time in seconds.

These experiments show, so far as drug experiments can be taken into account, that ventricular fibrillation under chloroform is essentially a sequence of a cardiac stimulation and occurs independently of a rise of blood pressure.

6. *Miscellaneous drugs.*

Atropine. The reaction of this drug is of considerable clinical interest, for it is frequently employed as a prophylactic against the cardiac effects of overdosage of chloroform. Under light chloroform anæsthesia in cats the intravenous injection of 0·6 mgms. of atropine sulphate caused a regular heart to pass into a persistent rapid irregular tachycardia ; a dose of 1·2 mgms. produced, in two experiments out of three in which it was employed, a permanent fibrillation of the ventricles in 70 seconds and in 3 minutes respectively. In the third case irregularities were produced and the heart fibrillated on exciting the sensory fibres of the sciatic nerve by cutting it, several minutes after the injection. In no case was the blood pressure raised as a result of the injection.

This reaction of atropine is in conformity with and confirms the result of section of the vagi under light chloroform anæsthesia, and may be referred to its power of paralysing the terminal vagal ganglia. I have employed atropine, administered by hypodermic injection in doses of about 0·1 mgms.,

in a considerable number of experiments on cats, and have generally found
a rapid and irregular heart to be the result.   For these reasons it would appear
that atropine would merely add to the dangers of the induction and lighter
stages of chloroform narcosis.

Curari.   I have observed ventricular fibrillation follow the intravenous
injection of 0·5 c.c. of a 2% solution of curari under 1% $CHCL_3$.   Otherwise
curari frequently makes the heart very irritable and liable to pass into
fibrillation, but its action is uncertain and at other times it has no effect in
this direction.   It is reasonable to attribute this action to the paralysing
effect which curari is held to exert upon the cardiac vagal ganglia.

SECTION II.—THE PRODUCTION OF CHANGES OF BLOOD PRESSURE WITHOUT
THE USE OF DRUGS.

1.   *Compression of the aorta.*

Of all methods employed for the purpose of raising the blood pressure
that of mechanical obstruction of the large arteries appears to be most free
from the complication of nervous disturbances.   It is true that the heart is
slowed, and this may be, as first suggested by Marey,[18] a vagal effect, but
in anæsthetised animals at least, it is not a very marked one.   Apart from
this no other action is exercised upon the heart so far as is known except that
of a raised intracardiac tension.

Hering[10] has described cardiac irregularities occurring under such
conditions ; he has shown that in curarised animals compression of the arch
of the aorta may give rise to ventricular extrasystoles occurring every second
or third beat (bigeminal and trigeminal).   In these experiments the central
nervous system was thrown out of action by depriving it of its blood supply,
and therefore the ventricular extrasystoles may be taken to be of purely
intrinsic origin.   Knoll[11] likewise came to the conclusion, as a result of an
investigation upon curarised rabbits, that a rise of blood pressure, induced
in various ways, reflex and direct, resulted in the production of bigeminal
beats due to extrasystoles, but neither of these observers noted any higher
grade of irregularities than these.

It appeared to me at one time highly probable that such irregularities
might in the lightly chloroformed heart pass into more complex stages and
eventually into ventricular fibrillation, but such has not proved to be the case.

I have applied compression to the aorta in anæsthetised cats in two
situations (i) just external to the left subilavian artery after exposure through
a " window " in the thorax ;   (ii) just above the cœliac axis, after exposure
by a retroperitoneal operation.   In the first case artificial respiration was
employed, in the second case it was unnecessary.

Compression was applied either by means of a special screw clamp
constructed on the principle of a lithotrite, or more conveniently by means

of a strip of tape passed under the artery and its ends drawn through a narrow glass tube ; by pulling on the ends of the tape and forcing the glass tube down on to the aorta, the latter became compressed between its mouth and the loop of the tape.

TABLE VIII.

Aortic compression under light chloroform anæsthesia (0·5 to 1·0°₀).

In each of these experiments a number of consecutive compressions were made, but no useful purpose would be served in recording the whole of the results. For purposes of brevity one or more typical results from each cat only are recorded ; where extrasystoles are noted these may or may not have been obtained more than once in the same animal ; where a regular heart is noted no extrasystoles were obtained from any of the compressions in that animal.

No.	Site of compression.	Rise of blood pressure in mm. Hg.		Rate of beat.		Remarks.
				Before Compression.	During Compression.	
		FROM 60 mm.	TO 81 mm.	per min. 180	per min. 180	
1	Abdominal	60 mm.	81 mm.	180	180	Heart beat regular throughout.
2	,,	131	148 ,,	135	120	Heart beat regular throughout.
3	,,	106 ,,	136 ,,	124	132	Bigeminæ during compression.
4	,,	92 ,,	116 ,,	140	110	Heart beat regular throughout
5a	,,	96 ,,	120 ,,	180	165	Before cutting vagi. Beat regular throughout.
5b	,,	96 ,,	120 ,,	210	210	After cutting vagi. Beat regular throughout.
6	Thoracic	97 ,,	121 ,,	105	105	Heart beat regular throughout.
7a	,,	96 ,,	130 ,,	150	144	Before cutting vagi. Bigeminæ appear on compression.
7b	,,	113 ,,	133 ,,	180	180	After cutting vagi. Two single extrasystoles on compression.
8	,,	119 ,,	134 ,,	130	105	Two single extrasystoles appear on compression.
9	,, ,,	78 ,,	96 ,,	160	160	Spontaneous bigeminæ before compression, unchanged on compression.
10a	,,	100 ,,	114 ,,	210	200	Before cutting vagi. Regular beat throughout.
10b	,,	100 ,,	140 ,,	220	240	After cutting vagi. Bigeminal beat appears at 116 mm., and disappears on further rise of pressure.

A series of ten experiments was performed on cats lightly anæsthetised with chloroform of from 1°₀ to 0·5°₀ strength (Table VIII). The rise of blood pressure was not as a rule very great, possibly owing to the considerable cardiac depression caused by the chloroform, for the rise of pressure under ether was considerably greater (Table IX). The highest rise of pressure obtained under chloroform was 40 mm. Hg., and the smallest measured 18 mm. Hg. ; the result did not appear to be materially influenced by the site of compression, whether abdominal or thoracic, the average rise being the same in the case of the two selected sites.

It is seen that a rise of blood pressure following compression of the aorta generally gives rise to some slowing of the heart beat in those cases in which the beat remains regular. This slowing is not observed after section of the vagi.

In four cats out of the series of ten, compression of the aorta was followed by the appearance of extrasystoles (Fig. 10).
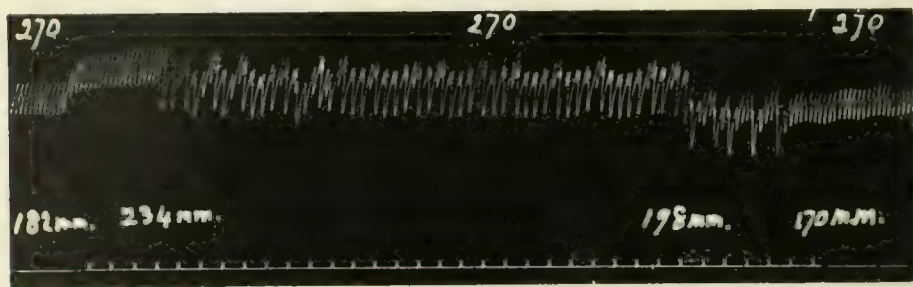
Fig. 11. × ¹⁰⁄₁₁. Compression of the thoracic aorta under light ether anæsthesia. A rise of blood pressure is followed by the appearance of a mixed bigeminal and trigeminal beat, which disappears shortly after decompression. Hürtle manometer. Time in seconds. The lower row of figures denotes blood pressure, the upper, rate of ventricular beat.

The relation of the occurrence of extrasystoles to the rise of blood pressure may be expressed thus :—

Blood pressure on compression of aorta.	All results.	Results with regular beat.	Results with extrasystoles.
Average rise of blood pressure	23·5 mm.	21 mm.	28 mm.
Average maximum blood pressure	122 mm.	114·5 mm.	134·5 mm.

It would thus appear that the appearance of extrasystoles is favoured by the greater heights of blood pressure, and to a less extent by the greater change of pressure ; the rule does not hold good for comparison between individual experiments.

Section of the vagi was performed in three cats, but in one of these only did this appear to favour the subsequent appearance of irregularities on compression, where none had been produced before section. It is notable that no ventricular disturbance of a higher degree than bigeminæ appeared in any case. It is also notable that in several of these cats in which a subsequent injection of adrenalin was made the ventricles fibrillated at a blood pressure even lower than that obtained by aortic compression.

A further series of eight experiments was performed on cats under ether narcosis.

TABLE IX.

Compression of the aorta under light ether anæsthesia. The experiments are recorded as noted in Table VIII.

No.	Site of compression.	Rise of blood pressure in mm. Hg.		Rate of beat		Remarks.
				Before compression per min.	During compression min.	
		FROM	TO			
1a	Abdominal	102 mm.	153 mm.	200	193	Before section of vagi. Beat regular throughout.
1b		102 „	152 „	225	225	After section of vagi. Beat regular throughout.
2a	„	96 „	150 „	220	220	Before vagal section. Beat regular throughout.
2b		132 „	180 „	250	250	After vagal section. Beat regular throughout.
3a	„	144 „	178 „	195	165	Before vagal section. Beat regular throughout.
3b (Fig. 11)		182 „	234 „	270	270	After vagal section. Bigeminæ and trigeminæ on compression.
4	Thoracic	99 „	148 „	190	190	After vagal section. Beat regular throughout.
5	„	114 „	160 „	240	192	A single extrasystole on compression.
6a	„	154 „	200 „	260	240	Before vagal section. Bigeminal beat on compression.
6b		84 „	160 „	250	260	After vagal section. Bigeminal beat on compression.
7a	„	96 „	136 „	165	150	Before vagal section. Beat regular throughout.
7b		100 „	150 „	190	180	After vagal section. Beat regular throughout.

The rate of heart beat, when this remained regular, was generally somewhat retarded ; after section of the vagi this retardation was not observed with the single exception of experiment No. 7, in which it is very slight.
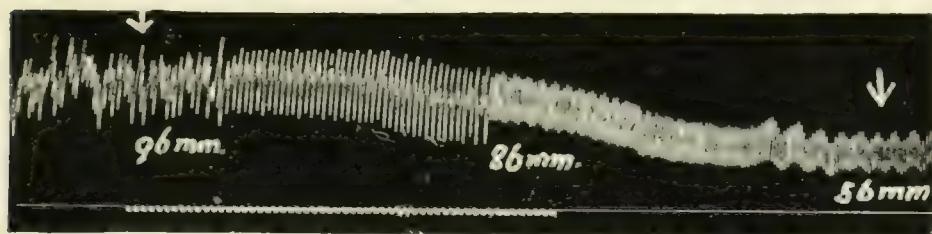
Fig. 12. Full size. The effect of a fall of pressure due to bleeding upon cardiac irregularities present in a cat under chloroform. Between the arrows the cat was bled 34 c.c. from the femoral artery ; as a result the highly irregular beat changes to a bigeminal condition and eventually becomes quite regular. 3 mgms. of atropine sulphate had previously been given by intravenous injection. Hürtle manometer. Time in seconds.

In three cats out of this series of seven, extrasystoles were observed on compressing the aorta, about the same proportion as obtained in the case

of the chloroformed cats—the irregularities were in some cases very well marked and made striking tracings (Fig. 11). The relation of the onset of extrasystoles to blood pressure under ether may be tabulated as follows :—

Blood pressure on compression of aorta.	All results.	Results with regular beat.	Results with extrasystoles.
Average rise of blood pressure	49 mm.	47 mm.	55 mm.
Average maximum blood pressure	167 mm.	156 mm.	188·5 mm.

Thus again there is strong evidence of a relation between the height of the final pressure and the degree of rise of pressure to the incidence of extra-systoles ; confirmatory evidence is afforded that a high blood pressure or a sudden rise of blood pressure, acting alone, will give rise to these ventricular irregularities, apart from any predisposing agent such as chloroform.

There is no evidence in the case of these ether experiments that section of the vagi has any appreciable effect in conducing to the appearance of these irregularities.

These experiments are important for they establish a difference between the extrasystoles produced by mechanically raising the blood pressure and those produced by a stimulation of the heart under chloroform, for the latter are not reproduced, or only in a modified form, under ether, and this fact would lead one to believe that pressure extrasystoles are of an essentially different class in relation to their genesis from those evolved from cardiac stimulations under chloroform alone. Moreover I have not observed any more complicated sequence of irregularities than those of a bigeminal beat as a result of aortic compressions ; the rapid multiple tachycardia is never seen, so that irregularities produced in this way do not admit of a passage into ventricular fibrillation. It is probable that simple extrasystoles from this cause have arisen and complicated the results of experiments involving a well marked rise of blood pressure in whatever fashion this is produced.

In view of the uncertainty of the experimental production of pressure extrasystoles, I have not investigated the influence of the nervous system any further, but having regard to the results obtained by Hering already referred to, there is no alternative but to accept these phenomena as purely pressure effects.

2. *The effect of bleeding from an artery.*

I have remarked elsewhere that spontaneous irregularities are less liable to occur when the blood pressure is below 100 mm. Hg.. Not only is this the case but existing irregularities are generally abolished when the circulation becomes depressed, as in the case of some loss of blood or from other causes. Fig. 12 shows the result of bleeding a cat to the extent of 34 c.c. ; the heart, which was originally irregular under 0.5% chloroform at a blood pressure
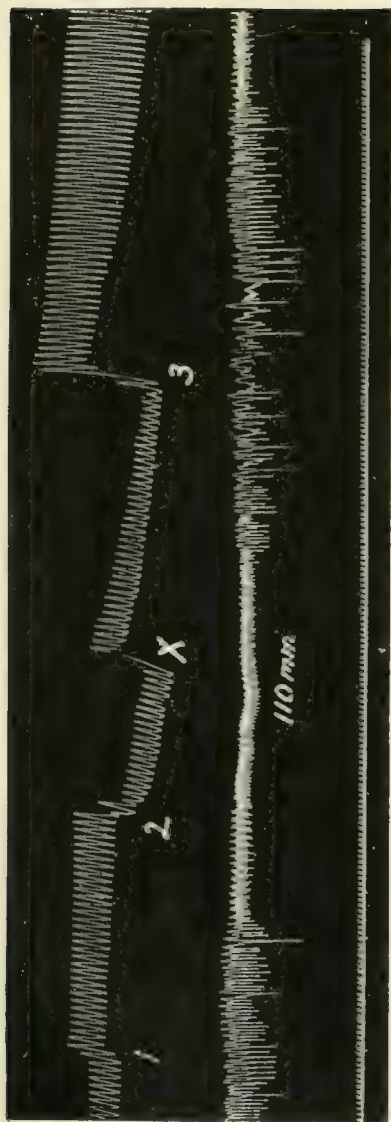
Fig. 13. × ¾. Showing the influence of varying the force of pulmonary perflation upon cardiac irregularities under chloroform.

1. Perflation increased, the irregular heart becomes regular.

2. Perflation decreased, irregularities reappear. (At × the respiration marker was adjusted, owing to a leak in the apparatus.)

3. Perflation increased, irregularities again disappear. Upper curve represents thoracic movements. Lower curve represents carotid blood pressure, mercurial manometer. Blood pressure abscissa omitted. Time in seconds

Fig. 14. Full size. The effect of pithing the spinal cord under 1% chloroform. Both vagi cut. The blood pressure rises, the heart becomes irregular and finally the ventricles fibrillate. The tracing is very similar to that of an adrenalin effect. Hürtle manometer. Time in seconds.

of 96 mm., became perfectly and permanently regular when the pressure had fallen to 86 mm.. In this experiment vagal action had been excluded by the intravenous injection of 3 mgms. of atropine sulphate, and the result is precisely similar to that seen in non-atropinised animals. It would appear therefore that, to some extent, the peripheral resistance has an influence upon the production of ventricular tachycardias and hence indirectly of fibrillation under chloroform, for a moderately high blood pressure is generally essential in order that the cardiac muscle may react.

The effect of bleeding appears to have a counterpart in the experiment of reducing the amount of blood in the heart by direct pressure on the heart. If the chest wall be gently squeezed over the position of the heart in a cat under chloroform, the blood pressure falls quite markedly and irregularities if present are almost infallibly abolished. Further the effect of artificial respiration, which has been already alluded to, probably comes under the same category. Spontaneous irregularities appear less frequently under artificial respiration, but when they do occur they may as a rule be abolished by increasing the force of the perflating blast. (Fig. 13.) The blood pressure may fall a little as a result, but usually this fall is small and probably the effect is exerted through setting up a positive intra-thoracic pressure, thus damming the blood back from the ventricles; Heger's[9] experiments leave no doubt that the blood supply of the ventricles is seriously diminished as a result of perflation of the lungs.

3.   *Pithing the spinal cord.*

Traumatic excitation of the spinal cord by pithing it occasions a considerable rise of blood pressure in cats lightly anæsthetised by chloroform. The action is complex, for the vaso-constrictor centres are not the only ones
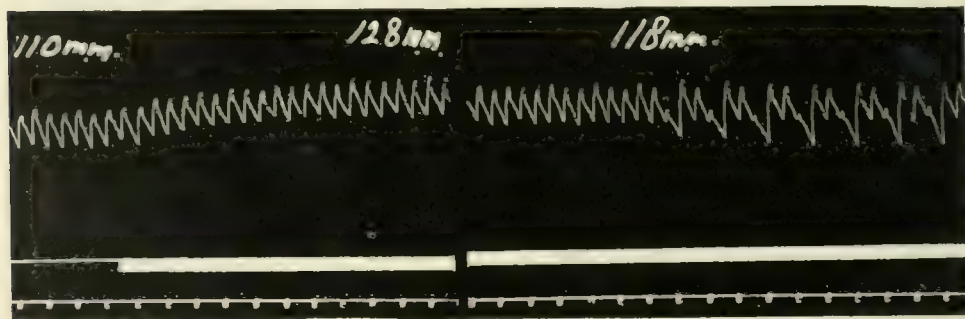
Fig. 15.   Full size.   Stimulation of splanchnic nerve in continuity in a cat under 0·5% chloroform after excision of both stellate ganglia and both suprarenal glands.   A series of trigeminal beats is thus produced which disappear shortly after the cessation of the stimulation.   The gap in the tracing represents an interval of 25 seconds.   Hürtle manometer.   The signal marks the period of excitation.   Time in seconds.

excited ; the heart and suprarenal bodies must be also stimulated through their sympathetic nerves, and it may likewise be accepted that impulses are initiated which ascend to the vagal centres in the bulb.

My procedure was to pass a flexible metal stylet down the spinal canal, introducing it through the occipito-atlantal space. In all the experiments herein described 1% of chloroform was administered, as this was found to be the most favourable strength for the production of ventricular fibrillation, whereas a lower concentration appeared less favourable, for what reason I cannot state ; 2%, as usual, inhibited fibrillation.

Out of four cats pithed with vagi intact under such circumstances, the heart passed through a temporary phase of tachycardia in all and ventricular fibrillation followed in one case only ; whereas, after cutting the vagi, ventricular fibrillation was obtained in a series of five consecutive experiments (Table X). The heart passed through a stage of multiple tachycardia before fibrillation occurred just as in the reaction to adrenalin (Fig. 14).

TABLE X.

Pithing spinal cord under 1% chloroform.   Both vagi cut.

No.	Vagi.	Respiration.	Blood pressure.		Result.
			Initial.	Maximum.	
A 1	Uncut	Natural	140 mm.	192 mm.	No V.F. Heart irregular.
2	,,	Artificial	130 ,,	160 ,,	No V.F. A short period of irregularity.
3	,,	,,	88 ,,	122 ,,	No V.F. A few irregular beats
4	,,	,,	116 ,,	141 ,,	V.F.
B 1	Cut	Natural	126 ,,	148 ,,	V.F.
2	,,	,,	118 ,,	150 ,,	V.F.
3	,,	Artificial	60 ,,	156 ,,	V-F., followed by recovery after 12 seconds.
4	,,	,,	143 ,,	164 ,,	V.F.
5	,,	,,	142 ,,	178 ,,	V.F.

The experiments afford an example of the influence which exaggerated vagal action exerts in preventing ventricular fibrillation, and they confirm my formerly recorded observations upon the relation of vagal action to ventricular fibrillation. The action is the antithesis of the effect of cutting out vagal action by section of the vagal nerve trunks.

These experiments were repeated on four animals under the influence of stronger chloroform vapour, and the results entirely confirm my conclusions that full percentages of chloroform prevent ventricular fibrillation. (Table XI.)

TABLE XI.

Pithing the spinal cord under 2% chloroform. Both vagi cut.

No.	Blood pressure.		Result	Remarks
	Initial.	Maximum.		
1	143 mm.	215 mm.	No V.F.	
2	168 ,,	204 ,,	,,	
3	106 ,,	146 ,,	,,	
4	108 ,,	183 ,,	V.F. of 3 seconds duration at 150 mm.	Under 2% for a short period only, and not deeply anæsthetised.

TABLE XII.

Pithing spinal cord under 1% chloroform. Both vagi cut. Surviving cats with cardiac accelerators cut or stellate ganglia excised.

No.	Respiration.	Blood pressure.		Result.
		Initial.	Maximum.	
1	Natural	134 mm.	146 mm.	No V.F.
2	,,	134 ,,	164 ,,	,,
3	,,	88 ,,	128 ,,	,,
4	Artificial	64 ,,	166 ,,	,,
5	,,	144 ,,	168 ,,	,,
6	,,	116 ,,	152 ,,	,,

The experiments were further repeated under 1% chloroform after section of both vagi and excision of the stellate ganglia or section of the cardiac accelerators. A well sustained irregular tachycardia was produced but in no case did the ventricles fibrillate. In the above series (Table XII) the conditions were identical with those of Table X (B), with the exception that the paths of direct cardiac stimulation were cut out ; the rise of blood pressure was well marked, a ventricular tachycardia was excited, doubtless through the excretory stimulation of the suprarenals, but the ventricles did not fibrillate, so that the paramount importance of the cardiac accelerator mechanism in the production of ventricular fibrillation by this method under chloroform is demonstrated. This series provides a parallel to the similar experiments performed with strychnine.

The blood pressure changes in the two series of experiments may be expressed in a tabular form ; the results as regards ventricular fibrillation are definitely positive and negative according as the cardiac accelerator mechanism is or is not intact, whilst the blood pressure changes approximate sufficiently to allow of their exclusion as a factor in the production of this phenomenon.

	In Table X (B). (V.F. constant).	In Table XII. (V.F. absent).
Average rise of blood pressure	41·4 mm.	41 mm.
Average maximum blood pressure	159 ,,	154 ,,

4.   *Excitation of sensory nerves.*

The production of ventricular tachycardias and fibrillation as an effect of reflex cardiac stimulation has been fully dealt with in a former paper. The pressor factor may be very briefly dealt with here. Some degree of rise of blood pressure was generally noted under chloroform, the maximum being 50 mm., but frequently the rise was insignificant or even absent, and it was evident that the degree of pressor effect bore no relation whatever to the incidence or intensity of the resulting ventricular tachycardias, and these are fully accounted for as the result of reflex cardiac stimulation.

By excluding the sources of reflex cardiac stimulation which I have recognised, namely, cardiac accelerator action and the suprarenal glands, I had looked to exclude all cardiac irregularities of reflex origin, but I did not consider the experiments then performed as being entirely free from a technical objection in relation to the regeneration of sympathetic fibres. The following experiment performed more recently is free from this objection and tends to confirm the fact that simple irregularities may result even after cutting out these reflex paths.

Experiment, April the 7th, 1913. *Cat.* Both stellate ganglia and one suprarenal body extirpated only twelve days previously. The remaining suprarenal now removed under chloroform and the right splanchnic nerve stimulated in continuity under 0·5% chloroform. The blood pressure rose from 110 mm. to 128 mm., the heart beat being unchanged and regular ; the pressure then slowly fell to 118 mm. when the beat changed to an orderly sequence of well marked trigeminæ which disappeared shortly after cessation of the stimulus (Fig. 15).

There can be no question here of a relation of the extrasystoles to pressor action, and the interpretation is, that a reflex secretion of a cardiac stimulant occurs, as already referred to in connection with the similar nicotine and strychnine reactions.

In cats treated by cerebral pithing and not under the influence of a general anæsthetic, sensory excitation gives rise to a far greater rise of blood pressure with slight cardiac acceleration ; generally the heart remains
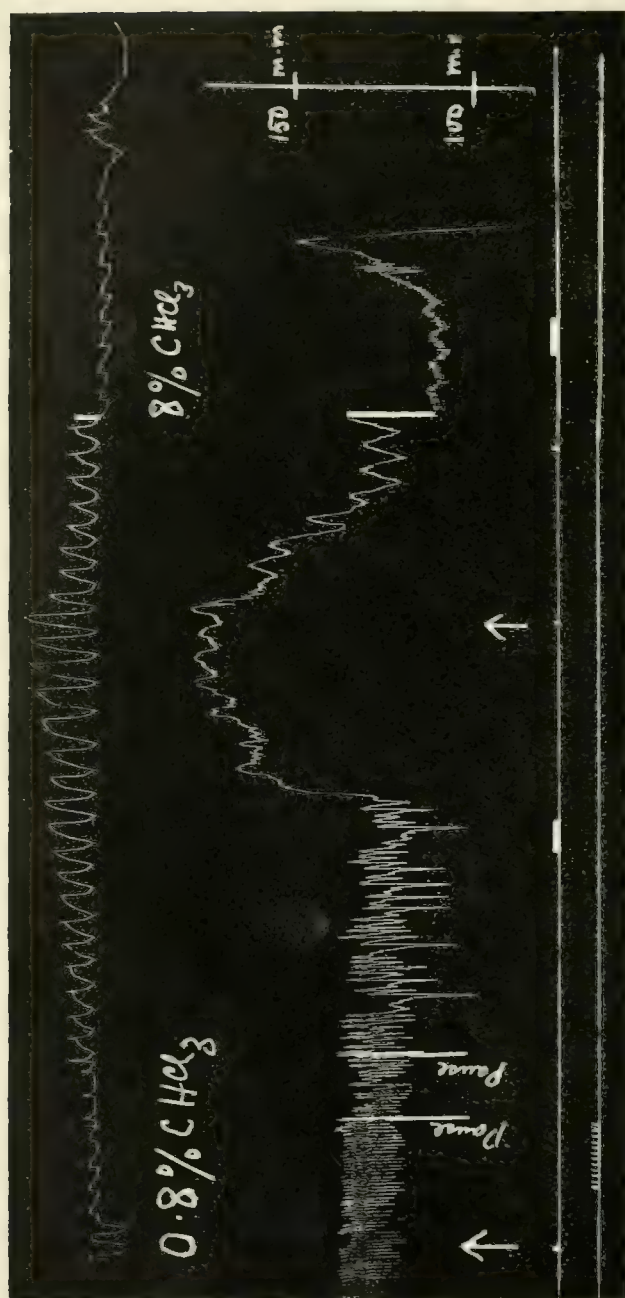
Fig. 16. Natural size. Asphyxia induced by rebreathing into a bag containing 0·8% chloroform. Both vagi cut and 0·2 mgms. atropine sulphate injected. The asphyxial process, continued between the arrows, causes the heart to become irregular; there is no rise of blood pressure. After 2 minutes asphyxia 0·065 mgms. of adrenalin were injected, which did not cause ventricular fibrillation. After recovery from asphyxia the same amount of adrenalin injected under the same percentage of CHCl₃ causes ventricular fibrillation in the usual manner. Upper curve respiratory. Lower curve blood pressure, mercurial manometer. The pressure abscissa is not shown. Time in seconds.

regular, but on giving chloroform and repeating the stimulation the normal typical rapid tachycardia results. In one instance (out of four experiments) I observed a trigeminal beat result from pinching the sciatic nerve in a cat not under chloroform, the blood pressure rising to 178 mm.; this in all probability being a pure pressor effect comparable to that obtained on compressing the aorta.

Under ether again very similar results were obtained. In three instances the blood pressure rose to a very high level (the maximum being 236 mm.) with a slightly accelerated though regular beat; an irregular tachycardia resulted after giving chloroform and repeating the excitation. In a fourth experiment under ether bigeminal beats appeared at a pressure of 196 mm.; this again without doubt being a pure pressor effect.

The rapid irregular tachycardia resulting from sensory stimulations is thus once again shown to be a specific effect of the chloroform.

5. *Stimulation of the stellate ganglion.*

A brief reference may be made to the relation of blood pressure changes to the production of ventricular fibrillation by stimulation of the right stellate ganglion, an experiment of fundamental importance in relation to my theory of cardiac stimulation under chloroform.

I have recently performed a fresh series of experiments upon six animals and ventricular fibrillation was obtained in four of these. A rise of blood pressure may result from the augmented action of the heart, but this is very variable and may be entirely absent; in the four successful experiments the blood pressure changes were as follows :—

TABLE XIII.

Blood pressure changes arising from stimulating the right stellate ganglion under low chloroform percentages.

No.	Blood pressure.	
	Initial.	Maximum preceding V.F.
1	110 mm.	112 mm.
2	104 ,,	104 ,,
3	68 ,,	142 ,,
4	66 ,,	94 ,,

Blood pressure changes being thus obviously excluded as a causal factor, in experiments Nos. 1 and 2, the significance of sympathetic nervous action is established.

Section III.

The Effect of asphyxial conditions.

The effect of asphyxia in relation to ventricular fibrillation under chloroform was investigated not only by reason of its physiological but especially on account of its clinical interest.

An asphyxial condition of the blood occasions a general vaso-constrictor effect by stimulation of the constrictor centres, but under a general anæsthetic, such as chloroform, there may be little or no rise of arterial blood pressure or indeed there may on occasion be a fall from the commencement as a result of the direct cardiac effect of asphyxia whereby the ventricles are dilated, and this effect is doubtless reinforced by the further cardiac dilating effect of the anæsthetic. These remarks hold true for experiments in which the vagi have or have not been cut. In the course of a former research[15] upon the action of asphyxia under chloroform I remarked upon the frequent incidence of cardiac irregularities under such conditions and their notable absence under ether anæsthesia, and these irregularities I can now identify as being precisely similar to those arising from cardiac stimulation under chloroform as by adrenalin, &c. No instance was observed at the time of actual cardiac syncope, but further research has shown that this may occur, as it did on a single occasion in which the blood pressure, following a phase of irregular tachycardia, fell to zero, recovery taking place after an interval of a few seconds. It is evident then that ventricular irregularities are the outcome of asphyxia under chloroform and may terminate in fibrillation as an exceedingly rare event.

The origin of these ventricular irregularities may be accounted for as a result of cardiac stimulation just as in the experiment of pithing the spinal cord or of injecting strychnine ; in each case there is a general convulsive nervous output, traversing the sympathetic system in common with the other efferent paths. That the heart is stimulated is evident from the acceleration observed in the spinal animal, and it is accelerated at the same time that it undergoes dilatation (Mathison[19]). This acceleration occurs after isolation of the heart from all nervous impulses, and it was therefore considered by Lehndorff[13] to be a cardiac response to increased peripheral resistance, but it may be inferred from the more recent experiments of von Anrep[1] that it is conditioned under such circumstances by an increased secretory activity of the suprarenal glands through their sympathetic innervation.* It would appear probable that the cardiac accelerator mechanism likewise comes into action during asphyxia, but I have not specially investigated this point, and it is sufficient for the present to point to the adrenalin effect as accounting for the onset of ventricular irregularities under chloroform.

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*Cannon and Hoskins· likewise conclude that asphyxia causes an increased suprarenal secretion.

TABLE XIV.

The injection of adrenalin in asphyxiated cats under the influence of low percentages of chloroform.

No.	Chloro-form.	Vagi.	Adrenalin.	Asphyxial condition.	Result.
1	0·8% 0·8%	Intact	0·065 mgms. 0·065 ,,	During asphyxia After recovery from asphyxia	No V.F. V.F.
2	1·0% 1·0%	Intact	0·065 mgms. 0·065 ,,	During asphyxia After recovery	No V.F. V.F.
3 (Fig. 16)	0·8% 0·8%	Cut Atropine sulphate 0·1 mgm.	0·065 mgms. 0·065 ,,	During asphyxia After recovery	No V.F. V.F.
4	?	Cut Atropine sulphate 0·1 mgm.	?	During asphyxia After recovery	No V.F. V.F.
5	0·8% 0·8%	Cut Atropine sulphate 0·1 mgm.	0·13 mgms. 0·13 ,,	During asphyxia After recovery	No V.F. No V.F.
6	0·8% 0·8%	Cut Atropine sulphate 0·1 mgm.	0·13 mgms. 0·13 ,,	During asphyxia After recovery	No V.F. No V.F.
7	0·8%	Cut Atropine sulphate 0·1 mgm.	0·065 mgms.	During asphyxia	V.F.

It can be shown by experiment that under asphyxial conditions the ventricles are in a great measure immune to ventricular fibrillation. In such experiments adrenalin was employed as a test stimulant ; the asphyxial condition was induced by attaching a small rubber bag, filled with air containing a small proportion of chloroform vapour, to a tracheal connecting tube, and allowing asphyxia to develop gradually by rebreathing of the contents ; the adrenalin was injected when the breathing became markedly dyspnœic, but before any pronounced fall of blood pressure had occurred.

It is thus seen that in one experiment alone out of seven did adrenalin cause ventricular fibrillation during asphyxia under chloroform ; whereas it was effective in two-thirds of the experiments after recovery from asphyxia. The protective influence is not derived through asphyxial stimulation of the vagal action ; it persists after cutting out all sources of vagal action, and it is reasonable to suppose that it is due to the direct action of asphyxia upon the heart, which it dilates, and such a supposition is in conformity with the like result observed from the action of glycolic acid, vagal action, and full doses of chloroform.

During recovery from asphyxia the heart passes through a stage of " passive stimulation," or recovery from depression, comparable to that caused by section of the vagi, and if the chloroform anæsthesia be very light, or if the chloroform be removed altogether at this stage, it seems reasonable to anticipate ventricular fibrillation may occasionally occur under such conditions.

<center>DISCUSSION.</center>

The relation of the single ventricular extrasystole to the complex ventricular tachycardias has been discussed in a former paper (Levy and Lewis[16]) and grades of ventricular disturbances forming connecting links between the two extreme conditions have been described. The intimate relation of the multiple ventricular tachycardia to ventricular fibrillation is not at present capable of direct demonstration, but it has been assumed that the latter is a still more advanced and complex grade of the former. Pending further light on this point it is possible to make the important statement that in every single instance of ventricular fibrillation induced under chloroform by any of the methods I have employed, it has been preceded by a stage of complex ventricular irregularities, so that unquestionably the one condition leads on to the other, whatever their relationship may be. This observation is limited for the moment to conditions in which the heart is affected by chloroform.

The liability of the ventricular extrasystoles to assume a complicated sequence would appear from my experiments to be governed by the conditions of their origin. Chloroform essentially favours their complication, but it has been shown how another form of simple rhythmic extrasystole, evoked by a mechanical increase of blood pressure and which is not dependent no chloroform poisoning for its appearance, has not shown any tendency to pass into more advanced grades of irregularity even when produced under chloroform narcosis. It is in fact probable that we are here dealing with extrasystoles of a distinct intrinsic genesis.

Apart from the experiments in which the blood pressure is raised by a method which involves an apparently purely mechanical affection of the heart, such as compression of the aorta, it is possible to trace in all the other pressor reactions I have described some factor effecting a cardiac stimulation, whether by direct muscular action, through the sympathetic nerves, or by an increased flow of adrenalin, and in view of the proved relation of cardiac stimulation under chloroform to ventricular extrasystoles and fibrillation, it is to this factor that we must look for an explanation of the ventricular disturbances. Not only do all my experiments mutually support one another in bearing this construction, but some of them afford distinct evidence that the blood pressure effect is entirely passive, at least in relation to ventricular fibrillation.

A theory of the protective action of full doses of chloroform against ventricular fibrillation previously advanced, namely, that it protects by depressing the ventricles, is in this paper amplified and justified by parallel

observations, and in this respect McWilliam's[20] contention that depressing influences are adverse to the production of ventricular fibrillation by direct faradization appears to be capable of extension. Depression of the ventricles may perhaps be better expressed in its more objective form, namely, dilatation ; glycolic acid and asphyxial blood, in common with full chloroform doses and vagal action, exert this effect to a notable degree, and with this common attribute a protective influence against ventricular fibrillation is connoted.

The protective influence of an increased action of the vagal mechanisms is more definitely illustrated in the experiments of pithing the spinal cord than in any other, although its influence was suspected in many circumstances.

That lowering the blood pressure will in itself conduce to abolishing pre-existing irregularities must be conceded, and this in the absence of vagal influences ; further at a low pressure the heart generally tends to remain regular, and it would be a simple view to adopt that a lowered pressure annuls the tendency which a raised pressure possesses of exciting extrasystoles. Such a view would not, however, be entirely satisfactory, for a lowered pressure, although it abolishes the simple rhythmic extrasystoles of raised intravascular tension, likewise abolishes the more intricate form of ventricular irregularities which are not excited by pressure changes. It would, I think, be safer to accept the generalisation, supported by other observations described in the body of the paper, that measures which tend to limit the blood supply to the heart reduce the liability to ventricular extrasystoles.

The study of these chloroform reactions has led to clinical conclusions of much practical importance in relation to the administration of chloroform as an anæsthetic ; at the same time it has led to an analysis of the factors favouring ventricular extrasystoles and fibrillation in the heart affected by chloroform, and these factors may be grouped as " predisposing " and " exciting." Whilst it is not possible to explain all conditions leading to ventricular fibrillation on the basis of these factors, yet it is at least probable that in the case of some drug actions and pathological processes they may be combined and exerted simultaneously, and it is on these lines that further research appears possible and desirable.

Conclusions.

1. Ventricular fibrillation is produced by cardiac stimulation under light chloroform anæsthesia independently of a rise of blood pressure.

2. Increased intraventricular tension may occasion the appearance of rhythmic ventricular extrasystoles. These are not a specific chloroform effect and have not been observed to lead to ventricular disturbances of a higher grade.

3. Measures which tend to diminish the volume of blood supplied to the heart are unfavourable to ventricular irregularities induced under chloroform. A certain degree of intracardiac vascular tension, about 100 mm. Hg. or over,

favours ventricular extrasystoles and fibrillation ; a lower tension is adverse to their existence.

4. Dilatation of the ventricles is a condition which is protective against ventricular fibrillation ; it is on this ground that the protective action of full doses of chloroform is explained.

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THE EFFECTS OF PREMATURE CONTRACTIONS IN VAGOTIMISED DOGS, WITH ESPECIAL REFERENCE TO ATRIO-VENTRICULAR RHYTHM.

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Introductory.

IN the present communication we discuss chiefly the effects of premature contractions upon atrio-ventricular rhythm as they have been observed in some recent experiments. We have used dogs exclusively and have made our observations in great part, upon animals which form the basis of another communication by one of us.[6] We have worked upon animals fully anæsthetised with morphia, paraldehyde and ether, in which both vagi were severed in the neck. The chest wall being opened, artificial respiration was in progress. For the method of producing atrio-ventricular rhythm and for a description of the method of recording the heart beat, we may refer to the same paper. Premature contractions were induced from various points by means of single induction shocks, at or about threshold value, and thrown into the heart at suitable intervals. We found at an early stage of the experiments that very exact measurements are required of the intervals of the curves. We have taken our records upon photographic plates and have measured our intervals on these plates by means of the Lucas comparator. Of these measurements a number of examples are given in the accompanying tables. We have paid considerable attention to the rate and uniformity of travel of our plates and the accuracy of our rotatory timemarker, measuring all time marks adjacent to points on the electrocardiogram in each of our curves. The chief source of error is in fixing the cross wires of the microscope upon the deflections measured. Magnified, the beginning of auricular deflections are often blunt, and the point taken is subject to choice within certain limits. But as a general rule the auricular complex shows in its initial phase some acute angle, notch or point, upon which cross wires may be fixed with considerable accuracy. The beginnings of the auricular complexes, which form one of the bases of our tables, have been corrected from additional measurements of this kind, and in this manner a changing error has been avoided very largely.

That is to say, although we may not be able to give the actual onset of an auricular complex with very great accuracy, the error in the interval between two complexes of the same kind is minute, for if there be a small error, it is maintained. In comparing successive intervals this method of mensuration has very obvious advantages. The error in fixing the onset of an auricular complex is small ; we take the actual onset at a calculated time from a given notch or angle, basing our calculation upon average measurements of the actual onset in the curve. We have used those curves only which provide sharp points for measurements ; consequently, every precaution has been taken to obtain electrocardiograms as smooth and uniform as possible. The measurement of excited contractions has called for additional care ; in most of our curves there is no trace of escape from the stimulating electrodes, a fact which has been ascertained by a comparison of make and break responses, and by searching the curves where break excitations fall in refractory periods.* But in all cases we have checked our measurements by comparing the sharp movement of the excitation signal. The great majority of our measurements have been repeated ; often by an independent observer.

Working in this fashion, we have reduced our errors of measurement to very small quantities, often the maximal error, as we calculate it from variations in timemarker, speed of plate travel and points chosen, amounts to one-thousandth of a second or less. The maximal error is certainly no greater in any case than four or five thousandths. The variation in successive and similar $P\text{-}R$ intervals in any table gives a fair idea of the maximal error. In our tables we have consequently given our figures to four places of decimals, so as to render the third place as accurate as possible.

Our measurements have been taken from electrocardiograms because these curves are of far greater accuracy than myocardiograms. We have almost always taken simultaneous curves directly from the muscle of the right appendix and across the ventricles, but the upstrokes of mechanical curves have no sharpness, the error in measurements is in hundredths and not thousandths of a second. Moreover, as has become plain to us, the myocardiogram introduces another source of inaccuracy when its curves are taken to indicate the onset of contractions. The interval which elapses between the onset of contraction in a chamber and the arrival of this contraction at the region to which the mechanical device is attached is by no means negligible. The error may amount to as much as four or more hundredths of a second, varying according to the relative position of the levers and onset of contraction and the size of the heart. An illustrative curve is shown in Fig. 4, where a contraction excited from the right appendix interrupts an atrio-ventricular rhythm. The points of onset of the auricular excitation waves are clearly marked in the electrocardiograms ; the $P\text{-}A$† distance for the atrio-ventricular beat is ·0510 seconds, for the appendix

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* Where the excitation shows it is clearly separate from the auricular complex

† Auricular complex to movement of auricular lever.

beat it is only ·0073 seconds. Our experience has convinced us that the complex effects of premature contractions cannot be studied with accuracy unless studied electrocardiographically, for the errors introduced in mechanical tracings are of a sufficiently high order to vitiate the results.

Our mechanical curves have served nevertheless as useful checks to the correct interpretation of the electric events.

Definitions.

In discussing the effects of premature contractions upon the rhythms which they disturb, it will be necessary for us to refer repeatedly to individual contractions of auricle or ventricle and to individual intervals between contractions. For the sake both of brevity and clearness we shall employ a fixed and simple terminology. The beats and cycles which precede a disturbance and which belong to the dominant rhythm we shall term the " initial beats " and " initial cycles " (Fig. 1, I.C.). The premature contraction we shall term the " forced beat," and shall apply this term to auricular (Fig. 1, F.B.) and ventricular systole without regard to the chamber in which such beat arises. The interval between the last initial beat and the forced beat will be referred to as the " forced cycle " (F.C.A. and F.C.V.). The contractions which follow the disturbance will be named " restored beats," the intervals between them the " restored cycles " (Rs. C.A.). The interval between forced beat and the first restored beat will be termed the " returning cycle " (R.C.A. and R.C.V.). The forced cycle and returning cycle will be referred to together as the " conjoined cycles " (C.C.). An *As-Vs.* or *Vs-As.* interval, will be qualified by the adjective attached to the *cycle* which it terminates.

1. THE EFFECTS OF PREMATURE AURICULAR CONTRACTIONS UPON *S-A* RHYTHM.

Our observations have been chiefly upon *A-V* rhythm, but we considered it desirable to have parallel observations upon *S-A* rhythm[*] in the same animals. We shall report these observations briefly, emphasising the fact that we are dealing with very accurate measurements.

Our curves show the events which are generally recognised to accompany premature auricular contractions. We have applied our excitations in the main at three points, namely to right and left appendices, and over inferior vena cava ; we have used the right appendix especially.

Changes in As-Vs intervals. The forced *As-Vs* interval varies with two factors. It varies according to the site at which the excitation is applied. It is longer when the right appendix is stimulated than when inferior cava is stimulated by some one or two hundredths of a second. These differences

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[*] So far as we are aware no systematic observations have as yet been made electrocardiographically.

we naturally attribute to the different lengths of muscle traversed. They might be used as actual measurements of the rate at which the excitation wave travels, but in practice we do not find them to be capable of sufficiently exact expression. We find clear evidence that the forced *As-Vs* interval is longer the more premature the forced beat ; a fact which is fully illustrated by our tables,* and which we believe has received no conclusive demonstration for the normally beating mammalian heart hitherto. The changes are small, being measured as a rule in one or two hundredths or in thousandths of a second. We find also invariable evidence of reduction of the returning *As-Vs* interval, unusually to be measured in hundredths (Fig. 2), usually in thousandths of a second ; there is occasional though inconstant evidence that this interval is shortest when the returning cycle is longest. The shortening may be confined to the returning *As-Vs* interval, it may also affect the succeeding interval, though this is rare.

Lengths of returning and restored cycles in auricle. The length of the returning cycle appears to be governed by several factors, the most important of which is the rate at which impulses are elaborated at the pacemaker. A change of original sinus rate immediately changes the length of returning pause *and by an approximately equivalent amount.* We consider that this fact has not received due emphasis in the past, for it clearly shows that the actual length of pause is governed in the main by the rate of impulse formation in the *S-A* node. It has been stated by Cushny and Matthews[1] and also by Hering[3] that the length of the returning pause is greater when the forced beat is more premature ; but we fail to find clear evidence for this statement in their curves. We have looked for a more precise change, namely, a change in the length of the returning cycle, relative to the initial cycles, and for this we have conclusive data. The range is however small, being measured often in thousandths of a second or at the most one, two, three or four hundredths. For reasons which we consider later we are not convinced that Wenckebach's explanation, namely, difference in the rate of conduction to the pacemaker accounts for these differences.

In calculating the actual excess of the returning cycle over an initial cycle, we have been surprised at the smallness of these values ; in stimulating right appendix or inferior vena cava they amount to no more than 3, 4 or 5 hundredths of a second as a general rule in medium sized dogs. On no occasion has the value exceeded the natural *As-Vs* interval for the same animal ; as a rule it does not reach to half this amount. We have measured the distances over which the contraction wave would travel by direct spread from the point of excitation to the pacemaker, and have calculated the approximate time which such contractions waves would take in travelling, on the basis of recent measurements of the speed of travel (Lewis[5]). These data are not sufficiently abundant for conclusive deductions,† but they are

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* Such few exceptions as are noted are covered by our error of measurement.

† We have recently investigated the point by more exact methods, and have been able to show a definite relation between excess of length of the returning cycle and the transmission time.

TABLE I. *S.A.* RHYTHM. STIMULATION OF AURICLE (SINGLE). 339

Dog.	Point of Stimulation.		Initial Cycles.		Forced Cycle.*	Returning Cycle.	Restored Cycles.			
EF. (1843)	Rt. app.	P-P	·7424	·7483	**·5618**	·7997	·7391	·7343	·7344	
		P-R	·1046	·1079	·1040	·1181	·1044	·1038	·1044	·1037
		R-R	·7457	·7444	·5759	·7860	·7385	·7349	·7337	
EF. (1843)	Rt. app.	P-P	·7900	·7916	**·5787**	·8549	·7903	·7936	·7927	
		P-R	·1053	·1060	·1060	·1141	·1024	·1084	·1093	·1060
		R-R	·7907	·7916	·5868	·8432	·7963	·7945	·7894	
EJ. (1945a)	Rt. app.	P-P	·5652	·5631	**·4092**	·6548	·5846	·5656		
		P-R	·1343	·1323	·1301	·1423	·1200	·1274	·1273	
		R-R	·5632	·5609	·4214	·6325	·5920	·5655		
EJ. (1945b)	Rt. app.	P-P	·5656	·5580	**·4961**	·6163	·5625	·5583		
		P-R	·1274	·1273	·1345	·1435	·1208	·1304	·1321	
		R-R	·5655	·5652	·5051	·5904	·5721	·5600		
EJ. (1970) Fig. 2	Inf. cav.	P-P	·6601	·6622	**·4211**	·7741	·6699	·6623		
		P-R	·1369	·1368	·1352	·1419	·0982	·1362	·1352	
		R-R	·6600	·6606	·4278	·7304	·7097	·6613		
EJ. (1963)	Inf. cav.	P-P	·6614	·6617	**·4617**	·7690	·6714	·6616	·6635	
		P-R	·1362	·1382	·1382	·1403	·1012	·1359	·1367	·1364
		R-R	·6634	·6617	·4638	·7299	·7061	·6624	·6632	
EL. (2039)	Rt. app.	P-P	·3243	·3207	**·1675**	·3658	·3280	·3194	·3213	
		P-R	·1039	·1034	·1051	·1525	·1047	·1047	·1040	·1038
		R-R	·3238	·3224	·2149	·3180	·3280	·3187	·3211	
EL. (2037b)	Rt. app.	P-P	·3145	·1353	**·2169**	·3594	·3184	·3137	·3156	
		P-R	·1051	·1042	·1047	·1282	·1047	·1063	·1055	·1043
		R-R	·3136	·3158	·2404	·3359	·3200	·3129	·3144	
EL. (2037a)	Rt. app.	P-P	·3143	·3151	**·2556**	·3531	·3151	·3156		
		P-R	·1038	·1048	·1055	·1180	·1043	·1059	·1056	
		R-R	·3153	·3158	·2681	·3394	·3167	·3153		
EL. (2050a)	Inf. cav.	P-P	·3675	·3670	**·2866**	·4164	·3683			
		P-R	·1069	·1076	·1073	·1040	·1046	·1064		
		R-R	·3682	·3667	·2833	·4170	·3701			
EL. (2048a)	Inf. cav.	P-P	·3600	·3601	**·3031**	·4039	·3578			
		P-R	·1089	·1082	·1081	·1031	·1039	·1093		
		R-R	·3593	·3600	·2981	·4047	·3632			
EL (2048b)	Inf. cav.	P-P	·3621	·3590	**·3230**	·3959	·3606			
		P-R	·1093	·1069	·1094	·1028	·1044	·1079		
		R-R	·3597	·3615	·3164	·3975	·3641			
EL. (2050b) (Fig. 5)	Inf. cav.	P-P	·3663	·3690	**·3340**	·3998	·3661	·3661		
		P-R	·1064	·1078	·1056	·1038	·1038	·1071	·1088	
		R-R	·3677	·3668	·3322	·3998	·3694	·3678		
EM. (2088a)	Rt. app.	P-P	·2989	·3019	**·2000**	·3534	·3047	·2993		
		P-R	·0989	·1022	·0981	·1302	·0995	·0981	·1015	
		R-R	·3022	·2978	·2321	·3227	·3033	·3027		
EM. (2088b)	Rt. app.	P-P	·2993	·3000	**·2266**	·3382	·3043	·3016		
		P-R	·1006	·1003	·1000	·1175	·1006	·1010	·1006	
		R-R	·2990	·2997	·2441	·3213	·3047	·3012		
EM. (2098b)	Rt. app.	P-P	·3028	·3052	**·2608**	·3293	·3043	·3043	·3027	
		P-R	·1036	·1028	·1032	·1076	·1012	·1037	·1027	·1033
		R-R	·3020	·3056	·2652	·3229	·3068	·3033	·3033	
EM. (2098a)	Rt. app.	P-P	·3018	·3035	**·2776**	·3239	·3044	·3038	·3030	
		P-R	·1005	·1004	·1000	·1055	·1004	·1026	·1026	·1016
		R-R	·3017	·3031	·2831	·3188	·3066	·3038	·3020	

* In this and subsequent tables the forced cycle is marked in heavy type in the auricular or ventricular line, according to the point of application of the stimulus.

TABLE II. S.A. RHYTHM. SINGLE AND SUCCESSIVE STIMULATION.

Dog.	Point of Stimulation.		Initial Cycles.	Forced Cycle.	Additional Forced Cycles.	Returning Cycle.	Restored Cycles.
EX. (2158)	Rt. app.	P-P	.3072	**.1857**		.3876	.3101 .3075 .0794
		P-R	.0822	.0800		.1347	.0802 .0814
		R-R	.3066	.2404		.3331	.3113 .3055
EX. (2153a)	Rt. app.	P-P	.3099	**.2320**		.3795	.3106 .3089 .3126 .3116
		P-R	.0808	.0798		.1260	.0772 .0796 .0798 .0799 .0801
		R-R	.3090	.2782		.3307	.3130 .3091 .3126 .3119
EX. (2153b)	Rt. app.	P-P	.3052	**.2482**	**.2611**	**1.5793** (6 cycles)	.3814	.3088 .3075 .3101 .3049 .3107
		P-R	.0791	.0823	.1000	.0998	.1025	.0751 .0779 .0790 .0791 .0800 .0813
		R-R	.3045	.2659	.2609	1.5820 (6 cycles)	.3340	.3116 .3086 .3102 .3058 .3120
EZ. (2186a)	Rt. app.	P-P	.4122	**.2400**		.4833	.4305 .4188 .4143 .4146
		P-R	.0767	.0780		.1036	.0798 .0784 .0779 .0767 .0771
		R-R	.4131	.2656		.4586	.4300 .4183 .4131 .4150
EZ. (2186c)	Rt. app.	P-P	.4221	**.2351**	**.2545** **.2540**	.4802	.4474 .4277 .4252 .4246
		P-R	.0781	.0764	.1024 .1028	.1027	.0775 .0685 .0673 .0711 .0715
		R-R	.4207	.2611	.2549 .2539	.4550	.4384 .4265 .4290 .4250
EZ. (2186b)	Rt. app.	P-P	.4214	**.2072**	**1.3951** (5 cycles)	.4901	.4383 .4278 .4209 .4222
		P-R	.0774	.0787	.1036	.1009	.0785 .0780 .0765 .0786 .0778
		R-R	.4222	.2321	1.3924 (5 cycles)	.4677	.4378 .4263 .4230 .4214
EZ. (2187b)	Rt. app.	P-P	.4703	**.3086**	**.8806** (3 cycles)	.5189	.4868 .4754 .4717 .4680
		P-R	.0809	.0802	.1021	.1035	.0893 .0875 .0868 .0866 .0883
		R-R	.4704	.3215	.8820 (3 cycles)	.5047	.4850 .4747 .4715 .4697
EZ. (2187a)	Rt. app.	P-P	.4699	**.3502**	**1.3323** (4 cycles)	.5206	.4761 .4759 .4715
		P-R	.0905	.0907	.1021	.1022	.0864 .0910 .0880 .0873
		R-R	.4699	.3616	1.3324 (4 cycles)	.5048	.4807 .4729 .4708
EZ. (2187c)	Rt. app.	P-P	.4754	**.4027**	**1.5002** (5 cycles)	.5395	.4978 .4887 .4751
		P-R	.0902	.0918	.1000	.1080	.0793 .0833 .0806 .0833
		R-R	.4747	.4109	1.5082 (5 cycles)	.5108	.5018 .4860 .4778

not incompatible with Wenckebach's view that the increased length of the returning pause is due in the main at least to the time lost while the contraction wave is travelling to the pacemaker.

For example in Table I, Curves 2037*a* and 2050*b*, the excess of the returning pause in the auricle over the initial pause is ·0384 seconds for right appendix stimulation, and ·0322 for inferior caval stimulation. The distance of these points from the upper end of the sulcus terminalis was, with the auricle in the diastolic position, approximately the same, namely, 30 mm.. In four animals, one of us found the average rate of conduction in the auricle to be 955 mm. per second ; the time taken to travel 30 mm. would be ·031 seconds, calculated upon this basis.

The first restored cycle is almost always longer than the initial cycles, but by trifling amounts (usually 3, 4 or 5 thousandths of a second, on one occasion it reached one hundredth, on another two hundredths of a second). It is possible, as Cushny[2] has suggested, that a retardation of the *S-A* impulse formation, produced by the premature beat may play some part in prolonging the returing cycle, but we think that evidence for this view is still lacking. It certainly appears to play little part in the vagotomised animal. As Table II shows the excess of the returning over initial cycles may be less after successive than after single interruptions ; although there may be more lengthening of the restored cycles in the first named circumstance.

The conjoined cycles are together shorter than two initial cycles in all our curves, with a few solitary exceptions to be subsequently considered ; they are shortest when the forced beat is most premature. The exceptions are instances where the contraction wave has evidently failed to reach the pacemaker. Of such curves we shall speak again.

2. THE EFFECT OF PREMATURE AURICULAR CONTRACTIONS UPON *A-V* RHYTHM.

Hering[4] and Rothberger and Winterberg[7] have already made some observations upon the effects of auricular extrasystoles upon *A-V* rhythm. These writers describe two forms of disturbance, one of which is limited to the auricle, the other affecting both chambers. In the former instance the ventricle is said to suffer no disturbance ; in the last instance it is stated that despite conduction to the lower chamber the returning pause may be compensatory. Hering used myocardiographic curves only, Rothberger and Winterberg employed electrocardiograms in addition. In both series of observations, attention appears to have been focussed upon the question of compensation. individual pauses have received no detailed analysis.

We may introduce the chief events by means of a figure (Fig. 3). In this figure the initial beats are of *A-V* nodal origin, the systoles of auricle and ventricle being almost simultaneous ; the interval is ·037 seconds. The premature contraction is excited from the inferior cava, and the *forced auricular beat* (F.B.) is followed by a *forced ventricular beat*. The lengths

of the forced cycles in auricle and ventricle are very different, and for the
reason that the relations of corresponding auricular and ventricular systole
are different. The forced cycle in the auricle is shorter than in the ventricle
by six hundredths of a second ; it is shorter by the forced *As-Vs* interval
less the last of the initial *As-Vs* intervals. Conversely, the *returning cycle*
in the auricle (R.C.A.) is longer than that in the ventricle (R.C.V.) ; it is
longer by the forced *As-Vs* interval less the returning *As-Vs* interval.

Forced cycle in auricle. It will be clear that the position of the forced
beat in the auricle is controlled absolutely by the excitation ; it may
commence at any period of the auricular diastole. Its position controls
the length of the forced auricular cycle.

Forced cycle in ventricle. The position of the forced ventricular beat is
controlled by the time at which excitation occurs and by the interval which
elapses between the excitation and the final response of the ventricle. This
interval is composed for the most part of the forced *As-Vs* interval. The
latency of the forced auricular contraction to stimulation we find to be very
constant in a given animal under the conditions of our experiments.

The length of the forced ventricular cycle depends therefore upon :—

1. The position of the last initial ventricular beat.

2. The time of excitation in relation to this beat.

3. The length of the forced *As-Vs* interval.

Forced As-Vs interval. We find this interval to vary appreciably in
different circumstances in the same animal. As might be expected from
similar changes in *S-A* rhythm, it is of greater length when the forced beat
comes early and of shorter length when this beat comes late in diastole.
The actual variation in length is definite, as the measurements given in our
tables show, it amounts to a few thousandths of a second in most experiments,
at the most to a few hundredths (Table III). Another factor which influences
the length of this interval is the position at which stimulation is applied to
the auricle. Evidently the time taken for contraction to travel from auricle
to ventricle must vary according to the point from which the contraction
starts ; it is chiefly a question of the degree of variation. We find that
the differences are measurable though they cannot be very accurately
expressed. Thus, in Table III (Dog EL.) the *As-Vs* interval for right
appendicular stimulation is approximately ·01 seconds longer than for
inferior caval stimulation ; compared with the normal *As-Vs* interval in the
same animal, the inferior caval *As-Vs* interval is reduced (see Table I,
Dog EL.) while the right appendicular *As-Vs* interval is a little increased.

TABLE III. A.V. RHYTHM. STIMULATION OF AURICLE (SINGLE). 343

Dog.	Point of Stimulation.		Initial Cycle.	Initial Cycle.	Forced Cycle.	Returning Cycle.	Restored Cycle.			
EE. (1822a)	Rt. app.	P-P	·6740	·6739	**4673**	·7756	·6709			
		P-R	·0565	·0589	·0607	·1169	·0606	·0606		
		R-R	·6764	·6757	·5235	·7193	·6709			
EE. ·1813	Rt. app.	P-P	·6940	·6912	**5119**	·7908	·6894	·6876	·6884	
		P-R	·0540	·0562	·0551	·1122	·0541	·0550	·0547	·0558
		R-R	·6932	·6901	·5690	·7327	·6903	·6873	·6895	
EE. (1822b)	Rt. app.	P-P	·6705	·6724	**6094**	·7308	·6721			
		P-R	·0606	·0619	·0596	·1106	·0589	·0603		
		R-R	·6718	·6701	·6604	·6791	·6735			
EF. (1850)	Rt. app.	P-P	·8397	·8368	**2869**	1·1174	·8498	·8431		
		P-R	—·0555	—·0575	—·0557	+·1155	—·0526	—·0540	—·0522	
		R-R	·8377	·8386	·4581	·9493	·8484	·8449		
EF. (1838)	Rt. app.	P-P	·8254	·8284	**3165**	1·0858	·8498	·8326		
		P-R	—·0519	—·0471	—·0463	+·0975	—·0521	—·0517	—·0475	
		R-R	·8302	·8292	·4603	·9362	·8502	·8368		
EJ. (1972)	Rt. app.	P-P	·6797	·6814	**3808**	·7754	·6887	·6905		
		P-R	·0880*	·0877	·0875	·1515	·0916	·0920	·0880	
		R-R	·6794	·6812	·4448	·7155	·6891	·6865		
EJ. (1981)	Rt. app.	P-P	·6864	·6880	**4320**	·7767	·6903	·6908		
		P-R	·0833	·0834	·0838	·1506	·0944	·0934	·0902	
		R-R	·6865	·6884	·4988	·7205	·6893	·6876		
EJ. (1975)	Rt. app.	P-P	·6893	·6868	**4811**	·7788	·6928	·6856		
		P-R	·0786	·0798	·0797	·1492	·0894	·0898	·0876	
		R-R	·6905	·6867	·5506	·7190	·6932	·6834		
EJ. (1967) (Fig. 21)	Inf. cav.	P-P	·7170	·7227	**4301**	·7612	·7143	·7180	·7017	
		P-R	·0961	·0855	·0471	·1395	·0958	·0886	·0568	·0506
		R-R	·7064	·6843	·5225	·7175	·7071	·6862	·6955	
EL. (2041)	Rt. app.	P-P	·4480	·4461	**2432**	·5165	·4509	·4496		
		P-R	·0335	·0334	·0328	·1129	·0417	·0378	·0334	
		R-R	·4479	·4455	·3233	·4453	·4470	·4452		
EL. (2044) (Fig. 4)	Rt. app.	P-P	·4557	·4567	**3108**	·5335	·4570	·4558	·4557	
		P-R	·0258	·0254	·0258	·1095	·0324	·0297	·0268	·0262
		R-R	·4553	·4571	·3945	·4564	·4543	·4529	·4551	
EL. (2043)	Rt. app.	P-P	·4477	·4476	**3675**	·5139	·4489	·4473	·4486	
		P-R	·0234	·0241	·0262	·1078	·0275	·0260	·0274	·0236
		R-R	·4484	·4497	·4491	·4336	·4474	·4487	·4448	
EL. (2053)	Inf. cav.	P-P	·5572	·5563	**2349**	·6320	·5686			
		P-R	·0397	·0398	·0385	·1099	·0431	·0366		
		R-R	·5573	·5550	·3063	·5652	·5621			
EL. (2054)	Inf. cav.	P-P	·5492	·5453	**2694**	·6178	·5630	·5470		
		P-R	·0352	·0350	·0354	·1026	·0442	·0371	·0372	
		R-R	·5490	·5457	·3366	·5594	·5559	·5471		
EL. (2052)	Inf. cav.	P-P	·5469	·5459	**3079**	·6144	·5556	·5479		
		P-R	·0337	·0340	·0371	·0975	·0407	·0378	·0354	
		R-R	·5472	·5490	·3683	·5576	·5527	·5455		
EL. (2051)	Inf. cav.	P-P	·5411	·5399	**3289**	·6126	·5536	·5422		
		P-R	·0367	·0376	·0394	·0984	·0413	·0387	·0379	
		R-R	·5420	·5417	·3879	·5555	·5510	·5414		
EM. (2085)	Rt. app.	P-P	·4294	·4308	**2870**	·5124	·4323	·4289	·4290	
		P-R	·0221	·0223	·0204	·1000	·0222	·0225	·0214	·0225
		R-R	·4296	·4289	·3666	·4346	·4326	·4278	·4301	
EM. (2084)	Rt. app.	P-P	·4344	·4295	**3413**	·5004	·4312	·4286		
		P-R	·0236·	·0212	·0242	·1033	·0236	·0228	·0237	
		R-R	·4320	·4325	·4204	·4207	·4304	·4295		

* The natural interval in this dog while A.V. nodal rhythm was present was approximately ·0460 seconds. In these curves higher values are seen because the stimulation was frequent and each premature beat was followed by increased intervals for *several* cycles (see Fig. 21).

TABLE IV. A.V. RHYTHM. SUCCESSIVE STIMULATION.

Dog.	Point Stimulated.	Rate and Duration of Tachycardia.		Returning Cycle.	Restored Cycle.								
EE. (1801) (Fig. 16)	Rt. app.	124 (4 min.)	P-P	·7488	·6545	·6577	·6570	·6631	·6708	·6711	·6736	·6762	·6786
			P-R	·1208	·0645	·0603	·0552	·0560	·0565	·0557	·0546	·0545	·0547
			R-R	·6925	·6503	·6526	·6578	·6636	·6700	·6700	·6735	·6704	·6797
EE. (1812) (Fig. 19)	Rt. vent.	142 (1¼ min.)	P-P	·6236*	·6683*	·6836*	·7320*	·7418	·7259	·7256	·7256	·7343	
			P-R	·1454	·0885	·0874	·0873	·0869	·0607	·0571	·0572	·0576	·0569
			R-R	·8575	·6672	·6835	·7325	·7156	·7223	·7257	·7260	·7336	
EE. (1803)	Rt. vent.	136 (¼ min.)	P-P	·7049	·6645	·6635	·6642	·6700	·6717	·6761	·6754	·6811	
			P-R	·1142	·0655	·0646	·0640	·0643	·0631	·0648	·0635	·0654	·0636
			R-R	·8846	·6636	·6629	·6645	·6688	·6734	·6748	·6773	·6703	
EF.‡ (1874) (Fig. 17)	Rt. app.	156	R-R	1·1236	·7629	·7399	·7321	·7325	·7289	·7265	·7248	·7211	·7230
EJ. (1943)	Rt. app.	159 (15 secs.)	P-P	·7080†	·6533†	·6650†	·6899†	·7187†	·7430	·7011	·7069	·7028	
			P-R	·1608	·1359	·1354	·1359	·1296	·0981	·0472	·0454	·0370	·0377
			R-R	·6831	·6528	·6655	·6832	·6872	·6921	·6963	·6985	·7035	
EJ. (1942) (Fig. 18)	Rt. app.	149 (15 secs.)	P-P	·7025†	·6311†	·6450†	·6811†	·6944†	·7256	·7298	·7010	·7009	
			P-R	·1559	·1305	·1371	·1395	·1328	·1322	·0808	·0519	·0408	·0335
			R-R	·6771	·6377	·6483	·6744	·6938	·6832	·6919	·6899	·6634	
EL. (2064)	Rt. app.	196 (40 secs.)	P-P	·5858§	·5336	·5140	·5177	·5172	·5177	·5162	·5150	·5150	
			P-R	·1053	·0472	·0340	·0350	·0341	·0333	·0329	·0321	·0320	
			R-R	·5254	·5204	·5150	·5168	·5164	·5173	·5154	·5149		
EL. (2045)	Rt. app.	202 (20 secs.)	P-P	·5665§	·5165	·5182	·5156	·5077	·5102	·5065	·5065		
			P-R	·0959	·0452	·0405	·0359	·0235	·0226	·0216	·0241	·0243	
			R-R	·5158	·5118	·5136	·5032	·5068	·5092	·5090	·5067		
EM. (2081)	Rt. app.	167 (15 secs.)	P-P	·4832	·4159	·4133	·4145	·4138	·4145	·4165	·4124	·4182	·4141
			P-R	·0970	·0260	·0239	·0226	·0214	·0227	·0235	·0235	·0245	·0224
			R-R	·4122	·4138	·4120	·4133	·4151	·4153	·4165	·4134	·4161	·4161

* *As* ending these cycles from a new focus.   ‡ Heart hypodynamic.   *P-P* could not be measured; *As-Ts* minute.

† These cycles were terminated by beats from the S-A node.

§ The *P* summit ending this the returning cycle was of different form.

The returning auricular cycle. This cycle (R.C.A.) is the longest of the disturbance. Compared with the corresponding cycle in the ventricle (R.C.V.) it is longer by the difference of the forced and returning *As-Vs* intervals. Its length relative to the corresponding ventricular cycle may be said to depend absolutely upon the lengths of these two intervals. Consequently, if we consider the factors influencing the length of the returning cycle in the ventricle it will suffice. But it may be well to emphasise at this stage the complexity of the factors which determine the duration of the returning auricular cycle : it cannot be compared to the similar cycle which follows a disturbance of the *S-A* rhythm nor can it be taken as a measure of impulse formation in the *A-V* node.

The returning ventricular cycle. This cycle is the most important and our discussion will centre around it, for in length it evidently gives with most accuracy the time which elapses between the disturbance of the *A-V* node and the completion of the next *A-V* impulse. This inter-ventricular interval represents the corresponding inter-nodal interval, providing that conduction is at the same rate from node to ventricle for the two beats which bound it. Such divergence as might occur between inter-nodal and inter-ventricular intervals would be in the direction of shortening of the latter, for the forced node to ventricular interval should be longer on account of its prematurity. The length of the ventricular returning cycle may be compared with that of initial ventricular cycles. We find that, relative to the last named, its length is variable within certain limits ; in the great majority of experiments it is prolonged (Table III), in exceptional cases it is sometimes prolonged and sometimes reduced. Where there is lengthening, this lengthening may amount to a few thousandths, or three or four hundredths of a second. In a solitary animal it amounted exceptionally to a tenth of a second. Where there has been a reduction of length, this reduction has amounted to a few thousandths of a second. Thus, the degree of lengthening or reduction, relative to the length of the initial cycle, is small. We may sum up in the statement that the returning cycle in the ventricle has approximately the same length as an initial cycle, but is usually subject to slight prolongation or exceptionally to slight reduction.

The actual length of the cycle is controlled by a single important factor, the rate of impulse formation in the *A-V* node. If the length of the cycle varies materially from time to time, a similar variation will be found in the initial cycles, clearly showing that the length depends upon the returning *A-V* automaticity.

The length of the returning ventricular cycle is not constantly influenced by the prematurity of the forced beat : but it is the rule that the more premature the beat the longer the returning pause. The variations are usually in thousandths of a second. The fact that conspicuous prematurity of the forced beat does not shorten the returning pause, as might be expected, but is usually accompanied by slight lengthening, leads us to the belief that the greater part of the ordinary increase in the forced *As-Vs* interval of conspicuously

premature beats occurs in the highest reaches of the node, or above the point at which the A-V rhythm originates ; for if it occurred in the lower reaches of the junctional tissues, it would surely shorten the pause in question. The observation that the returning pause in S-A rhythm and A-V rhythm is similarly affected by the degree of prematurity of the forced beat, is opposed to Wenckebach's view in respect of interruptions of the first rhythm. For if his explanation, that the difference is due to variations in conduction time from point stimulated to S-A node, were applied to A-V rhythm, then increased prematurity of a forced beat interrupting the last-named rhythm, should have no effect upon the returning pause or should shorten it.

The length of the returning cycle is uninfluenced by the site of stimulation. This is as might be anticipated, for variations of the time relations due to this cause are evidently in the transmission from excitation point to A-V node and not in the transmission time on the ventricular side of the A-V node. There are other factors which might possibly affect the returning cycle, but these will be discussed more conveniently at a later stage.

The returning As-Vs interval. This interval is subject to considerable change. It is the rule to find, not shortening as in interruptions of the S-A rhythm, but noticeable lengthening. This fact is clearly illustrated by our tables and is very distinct in Fig. 21.

The lengthening may amount to four or more thousandths of a second and sometimes to several hundredths of a second (Fig. 21) and may be spread over a number of cycles. In such circumstances and if the premature beats occur frequently the natural As-Vs interval may be concealed. Thus in Fig. 21 the natural interval for an A-V beat was ·040 seconds; but frequent extrasystoles kept it prolonged to values of ·09, ·08 and ·07 seconds (see Dog EJ., Table III). In some instances there is practically no change ; in some animals there is reduction. It is a very noticeable fact that the instances of no change or of reduction occur in animals in which the original As-Vs interval (of A-V rhythm) is relatively long.

The usual lengthening of this interval is, so we consider, the result of *bettered* conduction through those portions of the junctional tissues which unite auricle and the seat of impulse formation. One of us has shown that vagal stimulation, which produces forward heart-block in S-A rhythm, produces a shortened As-Vs interval during nodal rhythm, and has argued that this change is the result of hindrance to conduction in the tissue between auricle and impulse centre. The lengthening of As-Vs interval after the returning cycle, we regard as the reverse of this phenomenon. Whereas, during S-A rhythm, the returning As-Vs interval is shortened, and this unquestionably as a result of bettered conduction, in A-V rhythm the interval is longer than usual, though, as we think, from the same primary cause. And support is lent to this view, since, when the A-V rhythm arises at low levels (witnessed by short initial intervals) the lengthening of the returning As-Vs interval is conspicuous. We cannot sufficiently emphasise the constancy

of our findings in one respect, and we have abundant material ; the direction in which this *As-Vs* interval changes is dependent upon its original length. If the interval is originally long and indicative of a high origin of the impulse, the change is in same direction as when *S-A* rhythm prevails ; if short and indicative of a low origin of the impulse, the change is always in the reverse direction. In the first instance the change is in tissue below, in the last, it is in tissue above the focus which starts the contraction. The difference is due not to differences in the site of changed conduction, but to the position of the automatic centre relative to this site. We have some fortunate observations from a single animal, which are exemplified in Table IX (Curves 2161*b* and 2169). In this experiment the level of the *A-V* rhythm altered during the course of the observations ; and we were able to obtain two series of curves from the same animal, showing the changes in the returning *As-Vs* interval under the two conditions. When the original interval was long, the returning interval showed shortening ; when the original interval was short, the returning interval showed lengthening.

The restored cycles. The first restored cycle generally shows slight lengthening as compared to the initial cycles. Exceptions have been witnessed in a few animals (Table III, Dog EE. and Table IX, Dog EX. and FA.). The lengthening and the shortening when it occurs, is of trifling amount, namely a few thousandths of a second. The lengthening is not maintained, the succeeding cycle fails to show it except in rare instances.

The conjoined cycles. The length of forced and returning cycle together, or as we term them, the conjoined cycles, is not materially different in auricle and ventricle, though usually somewhat longer in the ventricle. This relative lengthening in the ventricle is evidently due to the customary increase of the returning *As-Vs* interval. If the returning interval is decreased, the conjoined cycles are longer in the auricle. In none of our experiments have we discovered the conjoined cycles to be equal in length to two initial cycles, except under the special circumstances where no forced ventricular beat occurs, a condition hereafter considered. Evidently since the returning cycle remains of almost constant length, the conjoined cycles vary in duration mainly according to the length of the forced cycle. The returning cycle may, it is true, almost compensate for the short forced cycle when the forced beat is late in diastole, even though the latter finds response in the ventricle. Thus in Table III, Curve 1822*b*, the figure for the conjoined cycles in the ventricle is 1·3395, while the two initial cycles total 1·3419 seconds. Here the difference is but two thousandths of a second, and it is evident that had the forced beat been still less premature the figures might have been equalised. But we regard the term compensatory, applied to any such phenomenon (Hering, Rothberger and Winterberg), as unfortunate,* since such restoration of the original

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* The compensation witnessed in these experiments may possibly be attributed to the non-section of the vagi.

rhythm, if it occurs, comes about in a totally different manner to that described by Engelmann, in observing the effect of ventricular extrasystoles upon *S-A* rhythm. It would not be due to the control of the length of the returning cycle by a dominant rhythm, but to a balance between its lengthening and the shortening of the forced cycle; the former being almost constant in a given animal, the balance is clearly a matter largely of coincidence. The possible restoration of the original rhythm in this manner, if it occurs, should not deflect attention from the essential question, the length of the returning cycle as opposed to that of the conjoined cycles.

Of compensatory pauses.

During S-A rhythm. As we have already stated, amongst our curves, we find no instances in which the conjoined cycles are equal to two initial cycles, with a few solitary exceptions. These are all disturbances in which the forced beat has fallen late in diastole. We publish two of our examples. The first is seen in Fig. 6. Here the forced auricular cycle (as measured

TABLE V.

(COMPENSATORY BEATS). *S-A* RHYTHM. INFERIOR CAVAL STIMULATION.

Dog.		Initial Cycles.		Forced Cycle.	Returning Cycle.	Restored Cycle.		
EL.	P-P	·3606	·3601	**·3514**	·3744	·3600		I.V.C. auricle precedes S-A auricle by ·009 seconds.
(2048)	P-R	·1044	·1079	·1083	·1073	·0167	·1075	
(Fig. 6)	R-R	·3641	·3605	·3504	·3738	·3608		
EL.	P-P	·3673	·3679	**·3679**	·3667	·3685	·3707	S-A auricle precedes
(2047)	P-R	·1044	·1065	·1054	·1045	·1083	·1077 ·1045	I.V.C. auricle by
(Fig. 7)	R-R	·3694	·3668	·3670	·3705	·3679	·3675	·0003 seconds.

TABLE VI.

(COMPENSATORY BEATS). *A-V* RHYTHM. STIMULATION OF RIGHT APPENDIX.

Dog.		Initial Cycles.		Forced Cycle.	Returning Cycle.	Restored Cycles.					
EL.	P-P	·4509	·4524	**·4055**	·4895	·4477	·4493				
(2040)	P-R	·0342	·0344	·0327	·0778	·0323	·0360	·0344			
(Fig. 8)	R-R	·4511	·4507	·4506	·4440	·4514	·4477				
EM.	P-P	·4183	·4183	**·3670**	·4602	·4188	·4176				
(2087)	P-R	·0234	·0207	·0204	·0700	·0230	·0212	·0203			
	R-R	·4156	·4189	·4166	·4132	·4170	·4167				
EX.	P-P	·4130	·4133	**·3531**	·4733	·4140	·4117				
(2161c)	P-R	·0355	·0378	·0372	·0999	·0380	·0387				
	R-R	·4153	·4127	·4158	·4114	·4147					
EX.	P-P	·3679	·3687	**·3163**	·4217	·3685	·3682	·3697	·3687	·3687	
(2165)	P-R	·0361	·0392	·0424	·0944	·0386	·0422	·0419	·0433	·0454	·0465
	R-R	·3710	·3719	·3683	·3659	·3721	·3679	·3711	·3708	·3698	
FB.	P-P	·4265	·4271	**·3668**	·4772	·4259	·4265	·4256	·4263		
(2206a)	P-R	·0375	·0369	·0370	·0922	·0380	·0366	·0364	·0364	·0358	
	R-R	·4259	·4272	·4220	·4230	·4245	·4263	·4256	·4257		

from excitation signal and actual onset of *P*) is ·3514 seconds ; the returning auricular cycle is ·3744 seconds. The initial cycles average ·3603 seconds. The major events are clear upon close examination of the curve. The auricular summit *P* of the forced beat is of unusual form : it is transitional between the normal *P* for this animal and the *P* excited from the inferior cava (see Fig. 5). The forced beat which occurs late in diastole has fallen one hundredth of a second earlier than the point at which the natural beat is expected : we have seen that in this animal the probable transmission time from inferior cava to pacemaker is three hundredths of a second (page 341) : insufficient time has elapsed for it to anticipate the natural beat at the pacemaker and consequently two waves of contraction have been propagated and have met in the auricular walls : hence the shape of the electric complex ; and hence the compensation, for impulse formation in the *S-A* node has remained undisturbed. We say undisturbed, but as a matter of fact it is very slightly delayed, for there is in reality a little over-compensation. To this overcompensation we shall refer again, trifling though it be. It is of interest to observe that although the forced beat in question failed to affect the sino-auricular node, it has affected the ventricle, for the corresponding ventricular beat is premature also.

For comparison with this curve we give another from the same animal (Fig. 7). Here again we are dealing with a beat forced from the inferior cava, but (again as calculated from the excitation signal) it starts at almost exactly the same instant as the expected natural beat. That is to say, it starts a little later than the forced beat of the last figure : *the corresponding electric curve consequently resembles the natural P more closely*, for the forced contraction* wave has had less start over the pacemaker contraction wave. Like the forced beat of Fig. 6 it has failed to reach the pacemaker, but as opposed to the last, it has also failed to affect the ventricle, whose beat falls at the natural time.† It is to be noted that the succeeding ventricular cycle is prolonged : true, the increase is within our maximal error of measurement, but in such disturbances the difference is always in the direction of lengthening. We are content at present to record the fact.

During A-V rhythm. A comparison of the curve which we now give (Fig. 8) with those of such figures as Fig. 3 and 4 should make it clear why, when premature auricular contractions disturb an *A-V* rhythm, there is no great range in the lengths of the forced ventricular cycles. Conduction being in the forward direction throughout for such forced beats, the forced ventricular cycle can never be so short as the forced auricular cycle. There is a difference in the range of lengths of the corresponding cycles for another reason ; a forced auricular beat may occur, as Rothberger and Winterberg

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* More correctly excitation wave, but it is convenient to speak of events in terms of contraction.

† Judged by *P-R* intervals in other curves from the same animal, transmission to the *A-V* node should be more rapid when the wave starts at the inferior cava than when it starts at the *S-A* node. We are consequently unable fully to account for the events of this curve.

have stated, so late in diastole that when it reaches the *A-V* tissues it finds them refractory. In these circumstances the returning ventricular cycle should be compensatory. We have not found it exactly so. In Fig. 8 it is less than compensatory by seven thousandths of a second, and this value is well outside our maximal error for this animal. The restored auricular cycles also show shortening, though in less degree. A precisely similar shortening of compensation is seen in each of our tabulated curves (Table VI).

We may not be able satisfactorily to account for this constant change, any more than we may be able to account for the reverse change where forced auricular beats fail to reach the sino-auricular node, but they serve definitely to show that although a forced contraction spreads over a limited area of the heart and does not actually reach the point from which impulses are generated, yet these forced beats may affect impulse formation in the dominating centre. We shall have occasion to note further examples of this phenomenon.

The origin of restored beats.

When *A-V* rhythm is disturbed by forced contractions, the restored beats show certain changes which we have noted already. The most noticeable event is a lengthening of the first *As-Vs* interval. This lengthening has been discussed and we regard it as the result of simple conduction change. This view is based largely upon the gradual change from longer interval to the original interval which occurs in some animals (see Fig. 21). From time to time and especially when the cooling of the *S-A* node is not great, another change is witnessed. It consists in the escape of the *S-A* node. An example is shown in Fig. 10. The first forced beat is followed by such an escape, after an interval of 1·0735 seconds, and this despite the length of the initial cycle which is 1·2690 seconds. Curiously the second forced beat of the same figure is followed by an atrio-ventricular contraction, although the returning cycle measures 1·3562 seconds. It is evident that the rate of impulse formation in the nodes has not remained constant, but that it has been disturbed by the occurrence of the forced beats. The more premature beat has quickened the *S-A* rhythm sufficiently to prevent its escape ; yet this quickening is but temporary, for immediately afterwards an *A-V* beat is preceded by a pause of 1·3415 seconds. We have seen numerous examples of similar changes in the rates of impulse formation and, as illustrated, they may follow single beats forced from auricle or ventricle. And the escape may not be confined to a single cycle, it may occur as in Fig. 9 and 14 for several successive cycles : ultimately the *A-V* rhythm is always restored. The escape, too, is not confined to the *S-A* node, it may be from other centres which we are unable accurately to locate. The reason of such escapes we shall consider more fully in the sequel.

3. THE EFFECTS OF PREMATURE VENTRICULAR CONTRACTIONS UPON A-V RHYTHM.

Hering and Rothberger and Winterberg have already recorded certain of these effects; we shall describe the disturbances in more detail. In these experiments we have adopted a single point of ventricular stimulation, namely, the infundibulum of the right ventricle.

In *A-V* rhythm the disturbances which happen in the heart when the ventricle is excited (Fig. 11 to 14) may be said to be similar to those which occur when the stimulation is auricular, if we may regard the heart beating in this fashion as consisting of two similar chambers *A* and *V*, lying on opposite sides of the *A-V* node, but with similar relations to it. At all events this statement is true for the major changes. *The forced cycle in the ventricle* is controlled in its length by the position of the forced beat, and this is governed by the moment of excitation. In most instances the forced ventricular beat creates an auricular response, just as the forced auricular beat creates a ventricular response. The length of the *forced cycle* in the auricle is fixed by the moment of excitation in relation to the last auricular beat and by the length of the forced *Vs-As* interval.

TABLE VII.

A-V RHYTHM. STIMULATION OF RIGHT VENTRICLE (SINGLE).

Dog.		Initial Cycles.		Forced Cycle.	Returning Cycle.	Restored Cycles.				
EC.	P-P	·4704	·4732	·4371	·4782	·4771	·4720	·4722	·4727	
(1748)	P-R	+·0427	·0417	·0401	—·0822	·0373	+·0378	·0406	·0408	—·0415
	R-R	·4694	·4716	**·3148**	·5977	·4776	·4748	·4724	·4734	
ED	P-P	·7591	·7593	·6133	·7791	·7693	·7601			
(1778)	P-R	+·0355	+·0338	+·0354	—·1588	·0327	+·0352	·0351		
	R-R	·7574	·7609	**·4191**	·9706	·7718	·7600			
ED.	P-P	·7601	·7549	·6555	·7690	·7609	·7665	·7452		
(1778b)	P-R	+·0352	+·0351	+·0343	—·1571	+·0315	+·0347	+·0330	+·0354	
	R-R	·7600	·7541	**·4641**	·9576	·7641	·7648	·7476		
EE.	P-P	·6518	·6517	·5405	·6909	·6431	·6515	·6498		
(1805)	P-R	+·0591	+·0549	+·0594	—·0958	+·0507	+·0572	+·0599	+·0568	
	R-R	·6476	·6562	**·3853**	·8374	·6496	·6542	·6467		
EE.	P-P	·6651	·6667	·5549	·7039	·6636	·6620			
(1791a)	P-R	+·0564	+·0596	·0547	—·0967	·0536	—·0548	·0555		
	R-R	·6683	·6618	**·4035**	·8542	·6648	·6627			
EE.	P-P	·6636	·6620	·6389	·6674	·6664	·6626	·6656		
(1791b)	P-R	+·0536	+·0548	+·0555	—·0929	+·0552	+·0570	+·0597	+·0590	
(Fig. 12)	R-R	·6648	·6627	**·4905**	·8255	·6682	·6653	·6649		
EZ.	P-P	·5925	·5904	·5676	·6084	·5942	·5939	·5902	·5908	
(2175)	P-R	+·0330	+·0329	+·0331	—·0809	+·0328	+·0328	+·0324	+·0324	
	R-R	·5926	·5906	**·4536**	·7221	·5944	·5933	·5902	·5908	

The forced Vs-As interval. In the case of auricular extrasystoles, we are able to give very accurate measurements; in the case of ventricular

extrasystoles we speak with more reserve in regard to the lengths of certain intervals and cycles. For the forced auricular contraction is represented by an electric complex which is buried in the electrocardiogram of the forced ventricular beat. It is not always possible to identify this auricular complex ; it is but occasionally that its onset can be estimated accurately. The electric complex of the auricle, responding on the one hand to a nodal impulse, on the other to a retrograde impulse from the ventricle, appears from a selection of our curves to be of constant form. In some instances, therefore, we are able to choose a notch or peak upon the retrograde complex and identify it with a similar notch or peak upon the nodal auricular complex (Fig. 12 and 14). In doing so we are guided to some extent by the intra-auricular distance as measured in the mechanically written curve. Each series of curves has to be regarded upon its intrinsic merits and while we are of opinion that the tabulated measurements which we publish are as accurate expressions as may be of the occurrences, we are somewhat more diffident in the conclusions which we draw from them, because of the difficulty in recognising the onset of the forced auricular beat with certainty. The main events, however, are perfectly clear.

In these experiments we find no conclusive evidence that forced Vs-As intervals are longer than forced As-Vs intervals. We have seen that the lengths of forced As-Vs intervals vary according to the site of stimulation of the auricle ; we may assume a similar variation in Vs-As intervals forced from various ventricular points. The duration of forward or backward conduction cannot be satisfactorily compared by our present methods ; especially is this true if the measurements are undertaken in mechanical curves ; for the As-Vs or Vs-As interval, at the case may be, expresses not only the conduction interval in one or other direction but the distance of the point stimulated from the conducting tissues, and also, in the case of mechanical curves, the distance of these tissues and the point of excitation from the recording levers. We are convinced that these factors are by no means immaterial. We are also unable to arrive at any final conclusion as to the effect of prematurity of the forced beat upon the length of the forced Vs-As interval. We do not consider our measurements to be sufficiently reliable in this respect.

The returning ventricular cycle. This cycle is the longest of the disturbance. Compared with the returning auricular cycle it is longer by the *sum* of the forced Vs-As and the returning As-Vs interval. Its length is controlled by these intervals and by the same factors which influence the returning auricular cycle, which we may proceed to discuss.

The returning auricular cycle. The length of this cycle evidently most closely corresponds to the interval elapsing between the disturbance of the A-V node and the completion of the next A-V impulse. It represents this internodal interval accurately, if conduction is at the same rate from node

to auricle for the two beats which bound it. And, as in the case of forced auricular beats, such divergence as might be expected would be in the direction of shortening of the inter-auricular cycle ; for the forced *Vs-As* interval should be relatively longer, in virtue of its prematurity. As a matter of fact, the inter-auricular cycle has been longer than the initial cycle by a few hundredths or thousandths of a second in all but one instance (Table X, Curve 2196).

The returning As-Vs interval. We have been able to detect no constant change in the length of this interval as compared with the initial intervals ; there is more often shortening than lengthening.

The restored cycles. The first restored cycle is usually lengthened by a few thousandths of a second, but sometimes it is shortened.

The *conjoined cycles* in the auricle have never been equal to two initial cycles, except when the forced ventricular contraction has failed to reach the auricle. The returning auricular cycle may be almost compensatory, as is the case in the ventricle when auricular contractions are forced. The two cycles are most nearly compensatory when the forced contraction comes late.

Of compensatory pauses.

When the forced ventricular beat comes so late in diastole that its retrograde impulse finds the node refractory, there may be compensation in the true sense of the term (Fig. 11). This phenomenon has been witnessed by Hering and Rothberger and Winterberg. We find some over-compensation by a few thousandths of a second. The rate of *A-V* nodal discharge is affected although the forced contraction wave from the ventricle does not reach this node. A disturbance, similar in some respects, was referred to under the effects of forced auricular contractions, but the direction of the change is different. With forced ventricular beats the nodal discharge slows, with forced auricular beats it quickens ; such at all events is our experience of compensatory beats. A curious example of compensation is seen in Fig. 13. If this figure is compared with Fig. 14 from the same animal, a conspicuous difference will be noted in the complexes of the forced ventricular beats. Yet stimulation was applied at the same ventricular point in each instance. In Fig. 13 the ventricular complex is transitional between the usual complex and that following stimulation of the infundibulum in this animal (Fig. 14). The forced beat is premature by but a few thousandths of a second. A contraction starts at the point of stimulation, but already an impulse is well on its way to the ventricle from the *A-V* node ; in the original curve the beginning of the usual auricular complex can be seen distinctly, immediately before the abrupt upstroke of the ventricular electrocardiogram. The two ventricular waves, the one following normal, the other abnormal, channels, meet in the ventricular walls.

TABLE VIII.

(COMPENSATORY BEATS). *A-V* RHYTHM. STIMULATION OF RIGHT VENTRICLE.

Dog.	Initial Cycles.			Forced Cycle.	Returning Cycle.	Restored Cycles.				
EC		·4645	·4647	·4640	·4710	·4654	·4674	·4648		
(1749) P-R		+·0399	+·0400	+·0393	—·0215	+·0401	+·0382	+·0357	+·0387	
R-R		·4646	·4640	**·4032**	·5326	·4635	·4649	·4678		
EE. P-P		·6468	·6485	·6487	·6508	·6485	·6491			
(1805) P-R		·0568	·0574	·0592	·0083	·0571	·0568	·0570		
(Fig. 11) R-R		·6474	·6503	**·5978**	·6996	·6482	·6493			
The same, but with the two excitation waves meeting in the ventricle.										
EZ. P-P	·5636	·5670	·5635	·5668	·5679	·5639	·5657	·5670	·5694	
(2179) P-R	·0307	·0313	·0298	·0309	·0159	·0299	·0313	·0314	·0299	·0296
(Fig. 13) R-R	·5642	·5655	·5646	**·5518**	·5819	·5653	·5658	·5655	·5691	
FB. P-P		·4098	·4055	·4101	·4077	·4098	·4057	·4093	·4076	
(2213) P-R		+·0313	+·0324	+·0350	—·0048	+·0313	+·0308	+·0339	+·0304	+·0319
R-R		·4109	·4081	**·3703**	·4438	·4093	·4088	·4058	·4091	

DISCUSSION AND FURTHER OBSERVATIONS.

We have seen that the length of the returning cycle, whatever its origin, is mainly controlled by the rate of impulse formation in the dominant centre. We have also seen that when *A-V* rhythm is disturbed, the cycle is usually slightly longer than an initial cycle. In this connection it is a matter of indifference whether the forced contraction comes from auricle or ventricle. It has been stated too, that this customary lengthening cannot be due to alterations in the conduction of impulses from node to auricle, or node to ventricle as the case may be, for such changes would tend to produce shortening and not lengthening of the returning cycle. In the hope of ascertaining the cause of the usual lengthening, we have studied the effects of rhythmic stimulation of auricle or ventricle upon the returning and restored cycles in the same animals.

Effects of rhythmic stimulation. We find that the after effects of rhythmic stimulation to be most inconstant from animal to animal, and to be extremely complex in one and the same animal. The lengths of the first few restored cycles are *usually reduced* by several hundredths of a second ; that is to say the re-awakened *A-V* rhythm is faster than before the disturbance. This fact is well illustrated in Table IX. Moreover it is the rule to find the rate *decreasing* as the rhythm becomes restored (Fig. 16, 18 and 19), until the previously established rate is resumed (see Table IV). In this respect *A-V* rhythm contrasts with the so-called idioventricular rhythm, which at its development is slow and increasing in rate as it developes. In a few experiments we have seen no alteration of rate as a result of the disturbance. In two exceptional instances (Fig. 17) we have seen a slower rhythm of development with a subsequent increase of rate, but in one of these the ventricle was exhibiting alternation. In other experiments, while the actual

rate at development was high, there was at first gradual quickening and eventually slowing. The duration and rate of the rhythmic stimulation appears to have no decided influence upon the events.

The returning cycle is as a rule increased in length, as compared to initial cycles ; rhythmic stimulation is usually followed in these animals by an *A-V* rhythm whose rate is enhanced but which is slowing. The returning cycle after a solitary excitation may be reduced in length, but these are not necessarily the experiments in which rhythmic stimulation accelerates the dominant rhythm. That the altered rate at which *A-V* impulses are elaborated, subsequent to rhythmic stimulation, influences the length of the cycle returning after such rhythmic stimulation would seem natural. Nevertheless we have not been able to show that such influence is material ; on the contrary our evidence is against its being so. Studying the lengths of the returning cycles following rhythmic stimulation, we find that they are usually reduced in length as compared to the returning cycle which follows a single forced beat ; a good example is seen in Fig. 15 where two forced beats are followed by a shorter returning cycle than is a single beat. But we have also seen instances where the returning cycle after rhythmic stimulation was longer than that following a single forced beat, and yet the restored cycles after rhythmic stimulation were at an enhanced rate. The effects of rhythmic stimulation fail to explain a lengthened returning cycle in vagotomised animals.

In one experiment, a rhythm of apparently high nodal origin was disturbed by rhythmic ventricular beats, excited as usual from the conus. These ventricular beats failed to affect the dominant rhythm (Fig. 20 and Table XI), and the auricle continued to beat in response to the dominant impulses. There was, for the time being, complete dissociation. Yet the rate of these dominant impulses rose during the stimulation and in some instances continued to rise subsequent to the termination of stimulation ; eventually they fell back to the previous rate. The influence of rhythmic stimulation may be an indirect one as this experiment shows, and is not necessarily the result of contraction waves reaching the dominant focus. These effects are comparable to the slight disturbance of accurate compensation where a forced auricular beat fails to reach the ventricle or where a forced ventricular beat fails to reach the auricle.

In many experiments rhythmic stimulation has resulted in alterations in the rate at which other centres elaborate their impulses ; notably the sino-auricular node. A succession of rhythmic contractions forced from auricle or ventricle may lead at its termination to the temporary dominance of the sino-auricular rhythm (see Fig. 18 and Tables) by increasing the rate of impulse formation at the natural pacemaker. The first few beats of the restored rhythm are from the sino-auricular node, beating, considering its continued cooled condition, at an unnaturally great rate ; this rhythm slows, and eventually the *A-V* node resumes its sway but also at an enhanced rate, which subsequently slows. We have seen precisely similar changes in the

TABLE IX.

A-V RHYTHM. SINGLE AND SUCCESSIVE STIMULATION OF RIGHT APPENDIX.

		Initial Cycles.		Forced Cycle.	Additional Forced Cycles.		Returning Cycle.	Restored Cycle.						
EE. (1811a) (Fig. 15)	P-P	·6606	·6656	·4291			·7746	·6624		·6577	·6556	·6591		
	P-R	·0556	·0575	·0578			·1264	·0570	·0589	·0612	·0612	·0591		
	R-R	·6685	·6659	·4977			·7061	·6634		·6577	·6535	·6584		
EE. (1811b) (Fig. 15)	P-P	·6624	·6599	·4401	·4440		·7638	·6541		·6577	·6556	·6591		
	P-R	·0579	·0589	·0607	·1258		·1304	·0583	·0612	·0612	·0612	·0591		
	R-R	·6634	·6617	·5052	·4486		·6927	·6560	·6577	·6577	·6535	·6584		
EJ. (1971)	P-P	·6806	·6779	·3405	·4076	2·7502 (7 cycles)	·7200*	·6583*	·6738*	·6852*	·7004	·7086		
	P-R	·0620	·0622	·0616	·1562	·1566	·1559	·1208	·1320	·1237	·1085	·0539		
	R-R	·6808	·6773	·4351	·4080	2·7495 (7 cycles)	·6939	·6605	·6655	·6700	·6765	·6869		
EX. (2161b)	P-P	·4130	·4139	·3034	·3004	·3006	·4934	·4137	·4124	·4165	·4146			
	P-R	·0390	·0379	·0356	·0619	·1272	·1221	·0411	·0407	·0405	·0389	·0355		
	R-R	·4119	·4116	·3902	·3657	·2408	·4121	·4133	·4122	·4149	·4112			
EX. (2149)	P-P	·3548	·3586	·2872	·3024	·9065 (3 cycles)	·4319	·3557	·3556	·3573	·3598	·3553		
	P-R	·0640	·0647	·0618	·0612	·1235	·1196	·0468	·0552	·0607	·0627	·0611	·0630	
	R-R	·3555	·3587	·3420	·3647	·9061 (3 cycles)	·3591	·3641	·3611	·3588	·3582	·3572		
EX. (2166)	P-P	·4198	·4209	·3993	·3004	·3006	·5081	·4222	·4189	·4192	·4192			
	P-R	·0405	·0398	·0401	·0619	·1272	·1264	·1430	·0400	·0400	·0400			
	R-R	·4191	·4212	·4211	·3657	·2408	·4247	·4192	·4189	·4194·				
EX. (2161a)	P-P	·4181	·4195	·3984	·3024	·9065 (3 cycles)	·4973	·4156	·4147	·4186	·4177			
	P-R	·0392	·0404	·0306	·0612	·1235	·1231	·0436	·0427	·0408	·0384	·0404		
	R-R	·4193	·4187	·4200	·3647	·9061 (3 cycles)	·4178	·4147	·4128	·4162	·4197			
EX. (2160)	P-P	·4130	·4109	·2755	·2928	·8783 (3 cycles)	·4963	·4076	·4075	·4080	·4094			
	P-R	·0409	·0409	·0412	·1264	·1284	·1323	·0440	·0403	·0400	·0415			
	R-R	·4130	·4112	·3607	·2948	·8822 (3 cycles)	·4080	·4039	·4072	·4095	·4093	·4114		
EZ. (2183c)	P-P	·4133	·4131	·2605			·5092	·4213	·4168	·4127				
	P-R	·0270	·0278	·0274			·0983	·0299	·0284	·0272	·0278			
	R-R	·4141	·4127	·3314			·4408	·4198	·4156	·4133				

EZ. (2183a)	P-P	·4267		·4287	·2798		·7403 (3 cycles)	·5314	·4351		·4273	·4271		
	P-R	·0288	·0286				·0974	·0993	·0317		·0290	·0282	·0291	
	R-R	·4267	·4285	·3486			·7422 (3 cycles)	·4638	·4324		·4265	·4280		
EZ. (2183b)	P-P	·4210	·4232	·2412		·9992 (4 cycles)	·5309	·4305	·4228	·4280				
	P-R	·0282	·0293	·0293		·1069	·1065	·0314	·0284	·0284				
	R-R	·4230	·4232	·3128		1·0048 (4 cycles)	·4558	·4275	·4224					
EZ. (2184c)	P-P	·4356	·4330	·3197			·4419	·4362	·4366	·4363	·4375			
	P-R	·0288	·0287	·0288			·0303	·0279	·0293	·0285	·0294	·0290		
	R-R	·4355	·4331	·3890			·4365	·4376	·4358	·4372	·4371			
EZ. (2184b)	P-P	·4306	·4296	·3883	·2511	·2496	·5370	·4429	·4293	·4327	·4289	·4295		
	P-R	·0297	·0297	·0301	·0687	·1009	·0885	·0334	·0302	·0301	·0308			
	R-R	·4306	·4290	·4270	·2833	·2472	·4719	·4410	·4295	·4331	·4276			
FA. (2202a)	P-P	·5896	·5837	·4407			·6325	·5697	·5640	·5611				
	P-R	·0884	·0871	·0875			·0986	·0885	·0886	·0882	·0878			
	R-R	·5883	·5851	·4508			·6224	·5702	·5636	·5637				
FA. (2204a)	P-P	·5035	·5021	·4098			·5387	·5834	·5847	·5576				
	P-R	·0864	·0866	·0860			·0868	·0872	·0812	·0864	·0864			
	R-R	·5931	·5019	·4200			·6271	·5824	·5869	·5876				
FA. (2202b)	P-P	·5480	·5482	·5462	·5265	1·4021 (5 cycles)	·5358	·5083	·5270	·5518				
	P-R	·0884	·0873	·0876	·0888	·0887	·0946	·0844	·0857	·0870	·0853			
	R-R	·5469	·5488	·5471	·5314	1·4030 (5 cycles)	·5256	·5046	·5283	·5501				
FA. (2204b)	P-P		·6356	·6282	·5800	1·4076 (5 cycles)	·6315	·5571	·6126	·6246				
	P-R		·0873	·0875	·0876	·0927	·0961	·0709	·0860	·0872	·0884			
	R-R	·6373	·6358	·6283	·5851	1·4113 (5 cycles)	·6180	·6632	·6138	·6258				
FB. (2206b)	P-P	·4310	·4328	·3301			·5099	·4206	·4333	·4327	·4313			
	P-R	·0315	·0326	·0322			·1140	·0362	·0328	·0334	·0315	·0296		
	R-R	·4321	·4324	·4119			·4321	·4262	·4339	·4308	·4294			
FB. (2208a)	P-P	·4299	·4258	·2924	·2309		·5264	·4309	·4299	·4258	·4289	·4304		
	P-R	·0308	·0304	·0313	·1221		·1355	·0438	·0370	·0385	·0320			
	R-R	·4295	·4267	·3832	·2443		·4317	·4331	·4264	·4273	·4283			
FB. (2206b)	P-P	·4279	·4265	·3794	·3590	·7171 (2 cycles)	·5036	·4317	·4284	·4275	·4262			
	P-R	·0372	·0368	·0363	·0855	·1118	·1109	·0159	·0380	·0380	·0376	·0364		
	R-R	·4275	·4280	·4286	·3853	·7162 (2 cycles)	·4386	·4218	·4274	·4271	·4280			

* The auricular contractions terminating these cycles were of S.-A nodal origin

TABLE X.

A-V RHYTHM. STIMULATION OF RIGHT VENTRICLE (SINGLE AND SUCCESSIVE).

		Initial Cycles.		Forced Cycle.	Additional Forced Cycles.	Returning Cycle.	Restored Cycles.				
FA (2196)	P-P	·5462	·5466	·5693		·5217	·5437	·5483	·5493	·5518	·5471
	P-R	+·0859	+·0880	+·0856		·1160 +·0865	·0860 + ·0880 + ·0867 + ·0887 + ·0847 + ·0855				
	R-R	·5463	·5492	·3677		·7242	·5432	·5450	·5483	·5505	·5482
FA (2194)	P-P	·5968	·6000	·5870	·3653 1·0957 (3 cycles)	·6317	·5812	·5948	·6000		
	P-R	+·0857	+·0865	+·0865	·0946	·1021 +·0882 + ·0889 + ·0884 1·0878					
	R-R	·5976	·6000	·4059	1·0898 (3 cycles) ·3637	·8220	·5849	·5943	·6665		
FB (2211b)	P-P	·4216	·4183	·3401		·4583 ·1235	·4184	·4186	·4193		
	P-R	+·0323	+·0332	+·0325		·0802 + ·0323 + ·0330 + ·0330 : ·0328					
	R-R	·4225	·4176	·2274		·5708	·4242	·4184	·4186	·4191	
FB (2210a)	P-P	·4216	·4206	·3598		·4349	·4216	·4230	·4200	·4200	
	P-R	+·0324	+·0313	+·0305		·0799 + ·0321 + ·0324 + ·0324 : ·0321					
	R-R	·4205	·4198	·2694		·5472	·4206	·4249	·4200	·4197	
FB (2214b)	P-P	·4539	·4547	·3460		·4853	·4567	·4578	·4199	·4553	
	P-R	+·0308	+·0313	+·0304		·0807 + ·0303 + ·0316 + ·0316 : ·0313 : ·0294					
	R-R	·4541	·4538	·2849		·5463	·4580	·4578	·4196	·4531	
FB (2210b)	P-P	·4228	·4190	·4201	·4160 (4 cycles) 1·3778	·4190	·4238	·4210	·4207		
	P-R	+·0311	+·0298	+·0304	·0000 ·0774	·0806 + ·0323 + ·0315 + ·0312 : ·0321					
	R-R	·4212	·4196	·3997	1·3746 (4 cycles) ·3386	·5619	·4233	·4204	·4216		

TABLE XI.

DOG FC. A-V RHYTHM. SUCCESSIVE STIMULATION OF RIGHT VENTRICLE.

		Initial Cycles.				Restored Cycles.										
(2234)	P-P	·5116	·5124	·5074	Tachycardia, right ventricle; rate 188; duration 15 seconds. ·5015	·5043	·5081	·5061	·5017	·5357	·5366	·5383	·5407	·5417	·5449
(Fig. 20)	P-R	·1102	·1104	·1090	·1100	·1115	·1125	·1122	·1110	·1099	·1092	·1110	·1113	·1108	·1099
	R-R	·5118	·5110	·5084	·3185 ·3207	·5758	·5091	·5044	·5049	·5346	·5350	·5401	·5410	·5412	·5440
(2235)	P-P	·6628	·6636	·6566	Tachycardia, right ventricle; rate 186; duration 15 seconds. ·6749	·6170	·6269	·6097	·6082	·6008	·6030	·6080	·6138	·6190	
	P-R	·0902	·0912	·0900	·0900	·1089	·0928	·0909	·0900	·0928	·0880	·0920	·0889	·0923	
	R-R	·6638	·6624	·6566	·4301 ·3218 ·3243	·6309	·6240	·6167	·6101	·6050	·6130	·6108	·6214		

case of centres which we are unable accurately to locate (Fig. 19) and similar changes although of a still more temporary kind may occur after single forced beats, as we have noticed. We ascribe these escapes to the same indirect quickening of the escaping centre which we have witnessed in the case of *A-V* rhythm.

Whether the reaction described is a sympathetic reflex or whether it is due to bettered nutrition as a result of raised heart rate, we have not attempted to determine. Sufficient, that the effects of rhythmic stimulation fails to help us in explaining the length of the returning cycle.

We may turn our attention to the lengths of the restored cycles following single forced contractions. When *S-A* rhythm prevails, these restored cycles are almost always longer than initial cycles, but as we have said there are exceptions. When *A-V* rhythm prevails they are usually lengthened, but frequently there may be shortening. Neither is there any constant relation between reduction or increase of the returning cycle and reduction or increase in the length of the restored cycle. We are forced to the conclusion therefore that the lengthening of a returning cycle has an independent cause and we apply this conclusion not only to *A-V* rhythm but to *S-A* rhythm also. In the latter case we believe, as already stated, that the position in which the forced beat arises sufficiently accounts for lengthening, in the case of *A-V* rhythm such an explanation does not hold, for we do not judge the length of the returning cycle by the contractions of the chamber from which the forced beat comes. If a forced auricular contraction disturbs an *A-V* impulse in the process of its creation, we should expect the subsequent impulse to be formed at the same rate : we judge of rate by measuring the interventricular interval. The returning cycle is found generally to be long by comparison with initial cycles, a similar lengthening may be found in the subsequent cycles ; yet the causes of lengthening in the returning and restored cycles appear to be distinct.

Our suggestion of the cause of lengthening in the returning cycle when it occurs is put forward tentatively : it may be explained if we suppose that the impulse centre is not immediately upon the path through which impulses pass from auricle to ventricle or ventricle to auricle ; that it lies a little way off this channel and that a little time is lost while the impulse is travelling to it, though meanwhile the same impulse is passing on to stimulate the second main heart chamber. The chief objection to this hypothesis is that it leaves no explanation of shortening of the returning cycle, when, as exceptionally is the case, this shortening occurs ; unless the centre is in these instances in the direct path.

Finally, we may revert to the question of the returning *As-Vs* interval. When we deal with an *A-V* rhythm in which the *As-Vs* interval is long the returning *As-Vs* interval is reduced in length. This reduction of interval, like the lengthening of interval when the initial *As-Vs* intervals are short, occurs although the pause preceding it is increased only by a few thousandths or a few hundredths of a second. Further, we have recorded instances of

change in this interval where the preceding pause is unaltered or very slightly shortened (for example, Curves 2161b and 2169, Table IX). The changes in the As-Vs intervals which accompany forced heart beats are almost universally ascribed solely to the changing periods of rest which the conducting tissues have enjoyed. In the light of our observations we find this view insufficient and cannot accept it in its entirety. Changes in the returning and restored As-Vs intervals are often conspicuous at the termination of rhythmic stimulation; they are usually more pronounced than after single interruptions. The direction of change is governed, as in the case of single beats, by the lengths of the initial intervals. After a number of rhythmic interruptions, and subsequent to a returning cycle which is conspicuously shortened (Curve 2202b, Table IX) the returning and restored As-Vs intervals may show decided shortening under suitable circumstances. The disturbing beat appears in itself to exercise a definite influence upon conduction as upon other functions of the heart; the channels through which such effects are produced are unknown to us; but it seems evident that the familiar formulæ of rest and recovery incompletely explain the phenomena witnessed. In this connection we may remember the recognised and profound effects which interpolated contractions of ventricular origin exert upon the succeeding As-Vs interval. Curiously, in our own series interruptions of a compensatory character have left this interval practically unchanged. The influence whatever it may be is, if not capricious, at least elusive.

Conclusions.

The following conclusions apply to the heart of the dog freed from central vagal control.

1. Premature contractions arising in the auricle and disturbing an S-A rhythm, are accompanied by changes in the As-Vs interval. The forced interval is lengthened, the returning interval is shortened.

2. When similar premature beats disturb an A-V rhythm, the returning As-Vs interval is lengthened, providing that the original As-Vs intervals are conspicuously short.

3. The change in the length of the returning interval is due in both instances to bettered conduction, the difference in the direction of the change in S-A rhythm and A-V rhythm being due to the relative positions of the automatic centre and the tissue in which the conduction changes occur.

4. The tissues whose conduction is chiefly affected by the disturbance of a premature contraction are the *A-V* nodal tissues or tissues in their immediate neighbourhood.

5. The length of the returning cycle, following an extrasystole, is chiefly controlled by the rate of the dominant rhythm which such extra-systoles disturb. The excess of the returning over the initial cycle increases as the forced beat is more premature, when a forced auricular beat disturbs an *S-A* rhythm, but not when it disturbs an *A-V* rhythm.

6. In the case of *A-V* rhythm, the excess is usually small, minute or absent. That is to say the length of the returning cycle is very close to that of an initial cycle.

7. It is the rule that in *A-V* rhythm, as in *S-A* rhythm, the greater the prematurity of a forced auricular contraction the larger is the returning ventricular cycle. This observation throws doubt upon Wenckebach's hypothesis, that the variation in the length of the returning cycle in *S-A* rhythm, results from variations in the rate of conduction.

8. We can find no evidence that extrasystoles by altering the rate of the dominant rhythm materially influence the length of the returning cycle.

9. In *A-V* rhythm the usual after-effect of rhythmic stimulation of the heart is an enhanced but reducing rate of stimulus production. This effect contrasts with that witnessed in the case of an idio-ventricular rhythm.

10. A forced contraction, or series of such beats, may influence the rate at which dominant impulses are elaborated, although the forced contractions fail to travel over the position of the dominant centre. This effect upon rate disturbs perfect compensation of the disturbance.

11. Compensation does not occur, except as a rare result of accidental balance, unless the forced contraction wave fails to reach the dominant centre.

12. It seems to us questionable that the formulæ of rest and recovery or want of rest and recovery completely account for changes in the *As-Vs* intervals which accompany extrasystolic disturbances of an otherwise regular heart action.

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·3005 ·3504 ·3738 ·3609

Fig. 6

·4055 ·4895 ·4477 ·4493

F·587 ·4506 ·4440 ·4574 ·4477

Fig. 8.

·7932 ·7939

·7605 ·7580

·0388 1·1584 ·0487 1·1473 ·0433

1·1583 1·1439

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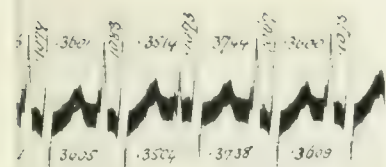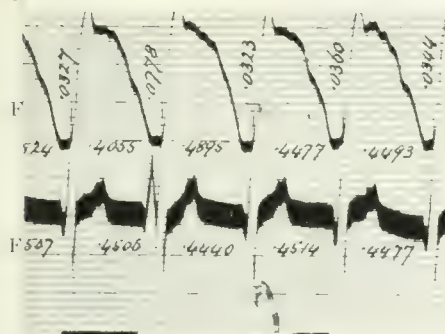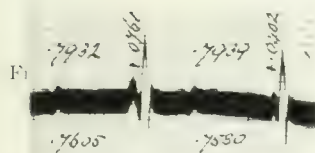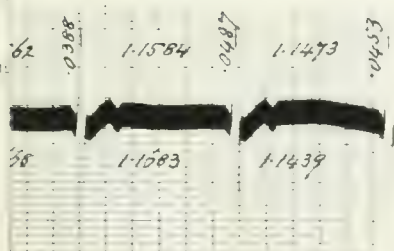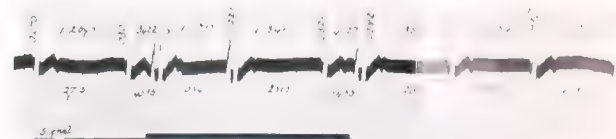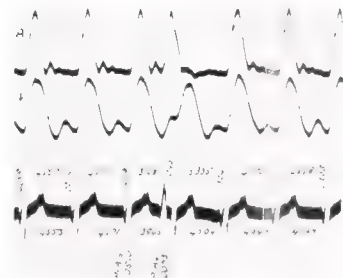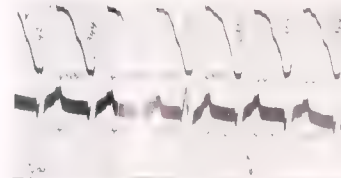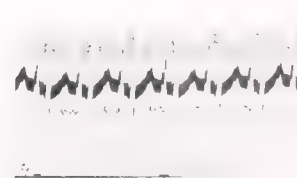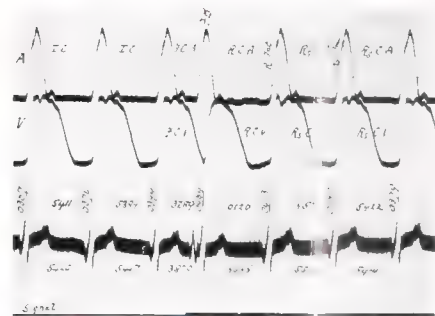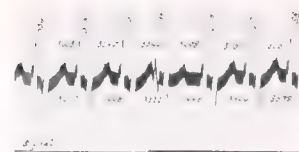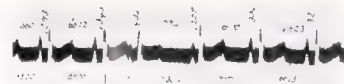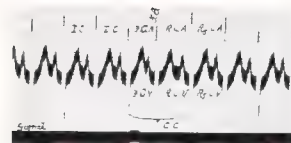
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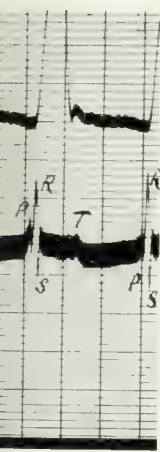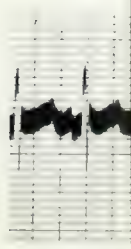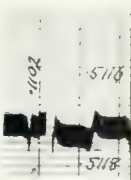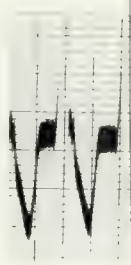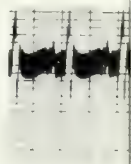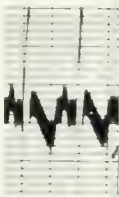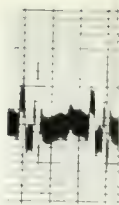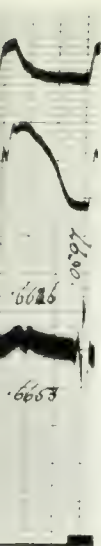
OBSERVATIONS UPON VENTRICULAR HYPERTROPHY, WITH ESPECIAL REFERENCE TO PREPONDERANCE OF ONE OR OTHER CHAMBER.

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THE observations contained in this report were undertaken from a special standpoint. It had been stated by Einthoven[1] that certain variations in the form of the human electrocardiogram, as it is seen in his three leads result from hypertrophy of the left or right ventricle, respectively. The view that preponderance of one or other ventricle may be recognised by means of these electrocardiographic signs seemed to me acceptable from my general experience of patients in whom the heart was hypertrophied ; Einthoven's statement seemed to obtain confirmation also from certain special observations. For in a series of cases of evident mitral stenosis, or in a series of cases presenting signs of congenital pulmonary stenosis, the curves of a right-sided preponderance were extremely frequent. In conjunction with Dr. White, late Obstetric Registrar at University College Hospital, I examined a number of new born children,[6] and found in these subjects that Einthoven's sign of right-sided preponderance of the heart is constant. Moreover, in extended observations upon two such children, we saw the curves gradually change, until they presented more natural relations at or about the third month of extrauterine life. Since Müller[8] has conclusively shown right-sided preponderance in the new born child and its gradual decline towards the third month, the evidence in favour of Einthoven's statement became stronger. Nevertheless, in a routine examination of a large number of cardiac patients, it has not infrequently happened that the curves obtained from patients in whom other physical signs pointed to preponderance of one or other ventricle disappointed the expectations raised by these signs. Thus, it happened, and not infrequently, that cases of evident mitral stenosis failed to show the sign of right-sided preponderance, or that cases with evident and free aortic regurgitation failed to present the electrocardiographic sign of left-sided preponderance. It seemed desirable consequently that more extensive observations should be made to determine the reasons for these apparent discordances.

Though this was the primary object of the research, once started it quickly extended beyond these limits, and became a more generalised inquiry into the relation of hypertrophy to valvular, renal disease and high blood pressure, and into the value of certain physical signs generally adopted as tests of unilateral increase of the heart muscle.

It was not until that portion of the work which deals with muscle weights had progressed for some while that I became aware of the extensive work of Müller upon somewhat similar lines. Becoming familiar with his observations, I saw no reason to alter my technique, which provides a more convenient and exact method than that described by him. Our observations do not seriously overlap, but where they do, the comparison is serviceable, because it shows that Müller's normal weights may be taken as a standard whichever method is adopted.

Observations.

Purely clinical observations.

In the first instance I collected clinical cases, exhibiting well-defined valve lesions, especially mitral stenosis, aortic disease and children with signs of pulmonary stenosis, and obtained from them standard electrocardiograms. These electrocardiograms were measured and the averages of each series were taken, so as to obtain type curves for the several forms of disease.

The general results of this investigation are found in Table I and Fig. 1. (The detailed results may be seen in Tables II to VI). The first table gives the average electrocardiographic measurements of the several deflections in six groups. The normal series is taken from my observations with Gilder,[7] observations which, according to Kahn,[4] are in close agreements with those of other observers. The chief and relevant conclusions of these observations may be stated. In mitral stenosis the average curve (Fig. 1) in lead I shows a diminution of R, and an increase of S; in lead III, a conspicuous increase of R and a decrease of S, as compared to the normal. This is the sign of right ventricular preponderance under discussion. But in a number of my cases the sign was not exhibited, and in a number it was exaggerated. In aortic cases the picture is reversed, for in lead I R is increased, and S diminished, while in lead III R is diminished and S is increased. These changes constitute the sign of left preponderance under discussion. Yet in aortic disease there were even more numerous exceptions to the rule than in mitral stenosis and on occasion the sign of right preponderance was exhibited.

In the congenital heart cases diagnosis was of necessity less certain, though here the average figures (Table I) speak for a much greater right-sided preponderance than in mitral stenosis. I have written briefly of these findings in my recent book " Clinical Electrocardiography " and have illustrated and emphasised the fact that it is in congenital pulmonary stenosis that Einthoven's sign of right preponderance is most fully developed.
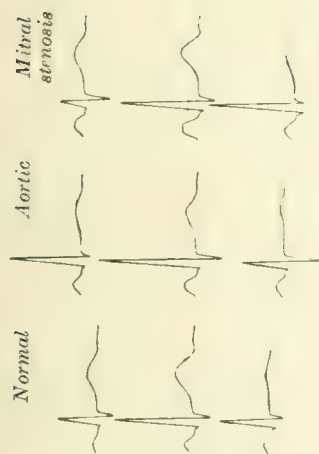
Fig. 1.

Average electrocardiogrammes in the normal subject, aortic disease and mitral stenosis. Ordinates 1 cm. 1 millivolt.

TABLE I.

A TABLE GIVING THE AVERAGE VALUES OF ELECTROCARDIOGRAPHIC DEFLECTIONS IN MILLIVOLTS.

	No. of Patients	Lead I.						Lead II.						Lead III.					
		P	Q	R	S	T	U	P	Q	R	S	T	U	P	Q	R	S	T	U
Normal	44	0·52	0·51	5·16	2·06	1·93	0·10	1·16	0·73	10·32	2·23	2·46	0·16	0·81	0·86	6·61	1·73	0·61	0·06
Mitral stenosis	40	1·17	0·34	3·05	3·47	1·47	0·10	2·05	0·84	11·17	2·09	2·49	0·30	1·15	1·30	11·27	1·25	1·16	0·09
Aortic regurgitation	31	1·05	0·54	9·31	1·37	0·87	0·02	1·57	0·62	11·67	3·57	1·40	0·11	0·94	0·61	5·37	5·79	0·65	0·06
Congenital disease	12	1·41	0·41	6·41	13·86	2·45	0·16	2·12	0·71	12·08	3·96	1·33	0·09	1·21	2·50	19·67	3·0	0·42	0·09
Renal disease	7	1·39	0·14	8·14	1·14	1·86	0·04	1·68	0·36	12·36	1·44	1·50	0·0	0·46	0·57	7·14	3·21	0·11	0·04
Mitral regurgitation	6	0·91	0·0	10·41	1·75	1·41	0·05	1·91	1·0	13·5	3·16	2·55	0·15	1·43	1·16	7·16	4·5	1·13	0·10

TABLE II. MITRAL STENOSIS.

	LEAD I.						LEAD II.						LEAD III.					
	P	Q	R	S	T	U	P	Q	R	S	T	U	P	Q	R	S	T	U
1	2·5	0	1·5	4	4	0	4*	1	5*	2	4	·3	1	·5	5*	0	1	0
2	·5	·5	2	2·5	1	0	2*	1	5	1	1·5	·3	2*	2	3*	·5	1	0
3	1	0	6	1·5	2	·5	2·5	·5	14	1	2	·3	1	1	6	0	1	0
4	1·5	·5	2	4*	2	·3	2·5	1·5	6·5*	·5	3	·5	1·5	2	9	·5	-1 +1	0
5	2	0	4	12	4	0	3*	1	7	11	3	·3	2*	3	16	6	·2 +1	0
6	1	0	2	2	2	0	3*	2	10	2	3·5	·5	2	1	9	1	1	0
7	1	1	2	2	·5	0	1*	1	8	2	1	·3	0	1	5	2	0	0
8	0	1	2	3	1	0	2*	1	10	0	2	0	2	2	10	0	1	0
9	1·5	1	4	4	3	0	2·5*	2	10	0	3	·3	1·5	2	10	0	1·5	0
10	1	0	2·0	2·5	2	0	2·5	1	18	1	4	·3	1	1	17	0	1	0
11	2	0	2	2	1	0	2*	1	11	2	2	·3	·5	1	11	1	—1	0
12	·5	0	1	2	1	0	2*	1	9	1	1	0	1*	·5	6*	0	1	0
13	1·5	0	9	·5	1	·5	1·5	1	18	1·5	4	1·1	—1	0	9	3	3	·5
14	1·5	1	2	1	1	0	1	·5	15	1	2	1·0	·5	1	16	1	2	0
15	1·5	1	6	0	1	0	2	1·5	14	1	2·5	0	1	0	9	2	2	1
16	·5	0	2	1·5	1	0	1	·5	11	2	2	1·1	1	·5	11	2·5	2	0
17	1*	0	1	3	0	0	2	1	15	2	3	·5	·5	1	18	·5	3	0
18	1*	0	2	4	1	0	1*	·5	13	1	3	0	·5	1	16	1	3	0
19	1·5	0	4	9	1	0	2·5*	·5	14	4	1·5 +1	0	2	4	22	1	·2	0
20	2*	0	2·5	1	2	·3	2*	1	16	3	7	·5	1*	2	17	3·5	6	1
21	1	1	4	3	2	0	2·5*	2	15	2	2	0	2·5	2	13	·5	2	0
22	1	0	1	4	·5	0	2·5*	1	14	3	3	·5	2*	2	16	0	—1 —2	0
23	2*	0	3	4	2	0	2	1·5*	13	3	1	0	1	2	16	1	—2	0
24	1*	0	2	2	1	0	2*	0	6	3	1	·3	1·5*	·5	5	2	1	0
25	2	1	5	12	2	0	2·5	1	8	2	4	0	1	4	12	2	0	0
26	1	1	5	1	1	0	1·5	1	13	1	1	0	1	1	10	1	1	0
27	0	0	1	1	1	0	1	·5	7	2·5	2	·3	·5	·5	7	2	1·5	0
28	1	·5	4	5·5	1	0	1	1	11	1	2	·3	0	2·5	15	1	1	0
29	1	0	1	2	1	0	2*	1	6	2	1	0	1*	2	7	2	—1	0
30	1	·5	1	4	1	·3	1·5	1	9	2	4	·5	·5	2	12·5	0	2·5	·3

TABLE II. MITRAL STENOSIS—*continued*.

	Lead I.						Lead II.						Lead III.					
	P	Q	R	S	T	U	P	Q	R	S	T	U	P	Q	R	S	T	U
31	1	0	2	1	1	0	2*	1	5	1·5	1	·3	2	2	7	3	1	0
32	2	·5	3	3·5	3	·3	3	·5	15	3·5	6	1·0	1	2	15	3	1	0
33	2	0	1·5	3	3	·5	3	0	3	2	3	·3	1·5	0	2·5*	·5	1	0
34	1	0	1·5	7	1	0	2·5	1	10	4	1	0	·5	1·5	8	0	5	0
35	1*	0	1	4	·3	0	1·5	·5	11	4	2	·5	1*	1	11	3	1·5*	·3
36	0	0	1·5	5	1·5	·5	3	0	13	0	3	0	3	·5	14	0	1·5	0
37	1	2	6*	0	1·5	·3	1	0	20	0	4·5	0	2*	0	19	2	2	0
38	1	0	7	6	·5	0	2	0	13*	2	1	0	1·5*	0	12	0	1	·5
39	1*	0	1·5	6	1	·5	1·5*	0	10·5	3	2	0	1*	0	16	0	1*	0
40	1	1	11	3·5	2	0	2	0	15+	3	2	·5	1·5	0	8	1·5	—1	0
Av.	1·17	·34	3·05	3·47	1·47	·10	2·05	·84	11·17	2·09	2·49	·30	1·15	1·30	11·27	1·25	1·16	·09

TABLE III. AORTIC REGURGITATION.

	Lead I.						Lead II.						Lead III.					
	P	Q	R	S	T	U	P	Q	R	S	T	U	P	Q	R	S	T	U
1	·5	3	14	2·5	1		1*	1	14	3	1		·5	0	3	3*	—1	
2	1	0	11*	3	1		2*	0	21	2	1		1·5*	1	10	1	1	
3	·5	·5	4	2·5	1		1	·3	6	2·5	2		·5*	0	2*	3*	·5	
4	1	·5	6	1	1		1·5*	·3	8	3·5	2		1	0	2*	4·5	—2 +1	
5	1	0	9*	·5	—1 +1		1	1	11*	1	—2 +1		1	2	5*	·5	—1	
6	·5	0	2·5	2	·5		2	0	15	1	2·5		2	1	15	·5	—2	
7	1	1	17	2	·5		1·5	·5	14	2	3		·5	0	1	7	2·5	
8	1·5*	·5	12	·5	1	0	2	1	8*	0	1·5	0	1*	0	1	7	0	0
9	·5	·5	7	2	0	0	1	·5	8	2	·5	0	·5	·5	2	1·5	1	0
10	1·5	2	5*	1·5	1·5	0	1·5*	2	17	1	4	·3	1	1·5	13	3	3	·3
11	1	·5	12	3	1·5	0	1·5*	·5	19	4	—1 +2	0	·5	0	5*	6	0	0
12	0	1	5	2	1	0	1·5	0	2	11	0	1·0	2	0	2	15	—2	·5
13	1	1	17	0	—2	0	2	0	16	2	—2	0	1	0	7	9	1	0

TABLE III.   Aortic regurgitation—*continued*.

	Lead I.						Lead II.						Lead III.					
	P	Q	R	S	T	U	P	Q	R	S	T	U	P	Q	R	S	T	U
14	1	1	9	2	·5	0	1·5	2	12	3	2	·3	1	1	2	4	2	·3
15	1·5	0	6	1·5	2	tr.	1·5	·5	5*	2·5	1·5	0	1	1	2	3*	—·5	0
16	·5	1	6	1·5	0	0	1·5	0	12	2	·5	0	·5	0	4	2·5	0	0
17	2	1	15	0	4	0	2	0	11*	0	7	0	1·5	0	1	6·5*	3	0
18	·5	·5	2	2	·5	0	1	·5	10	8	1·5	·3	·5	0	5	7	1	0
19	2	0	3	1	2	0	2*	·5	11	5	5	·3	1·5	1	8	8	3	·3
20	1	0	9	2	1	0	1	1	19	2	1	·3	1	1	10	2	1	0
21	2	1	11	2	3	0	3	2	22	17	5	0	2	1	10	17	3	0
22	·5	·3	11	0	1	0	1*	0	10	·3	1	0	·75	0	1	3*	·3	0
23	1*	0	8*	2	1·5	0	1·5	0	10*	0	—4	0	1	4	8*	0	-2·5	0
24	1·5	0	26	0	—4	·3	4	0	8	9	2	0	1	0	2	26	3	0
25	1	0	7	0	1	0	2	1·3	10	2·5	2	0	1*	1·5	7	4	1	0
26	1*	0	3·5*	0	·5	0	1*	0	14	8	2	·5	1·5*	0	10·5	9	1	0
27	·5	0	10	3·5	—1	0	·8	1	8	6	1	0	—1*	1	2·5	6	·5	0
28	1*	0	7*	0	·5	0	1·5*	1	2·5*	5·5	1·5	·3	2·5*	0	8	2	-1·0	0
29	1	1·5	14+	·5	2	0	1·5	·5	15	2	2	0	—1	0	2	15	·5	0
30	1·5	0	10	2	2·5	0	1	0	8·5	1	1·5	0	·5	0	9	1	2	0
31	2	0	9·5	0	2	0	1·5	2	14	2	3·5	0	1	1·5	6·5	2·5	1	·5
Av.	1·05	0·54	9·31	1·37	0·87	0·02	1·57	0·62	11·67	3·57	1·40	0·11	0·94	0·61	5·37	5·79	0·65	0·06

TABLE IV.   Mitral regurgitation.

	Lead I.						Lead II.						Lead III.					
	P	Q	R	S	T	U	P	Q	R	S	T	U	P	Q	R	S	T	U
1	1*	0	7	1·5	1	0	4·5	5	2 0	5	4	0	5*	5	17	8	3	0
2	1*	0	13	0	·5	0	1*	0	7	3	·3	0	1·3*	0	1	10	·3	0
3	1*	0	11	2	2·5	·3	2*	0	14	3	4·5	·3	1*	0	6*	0	2	·3
4	1*	0	11*	0	1·5	0	1*	0	12*	0	1	0	·5*	0	4*	4	—·5	0
5	·5*	0	12	0	1	0	1·5*	0	14	4	2	·3	·5*	0	5*	5*	1	0
6	1	0	8·5	7	2	0	1·5	1	14	4	3·5	·3	·3	2	10	0	1	·3
Av.	·91	0	10·41	1·75	1·41	·05	1·91	1·0	13·5	3·16	2·55	·15	1·43	1·16	7·16	4·5	1·13	0·1

TABLE V. RENAL.

	LEAD I.						LEAD II.						LEAD III.					
	P	Q	R	S	T	U	P	Q	R	S	T	U	P	Q	R	S	T	U
1	·75	0	5	2·5	2	0	2	0	7·5*	0	3	0	1·5	0	5*	0	1	0
2	1·5*	1	10	2	4	·3	2	·5	16	1	2	0	1*	1·5	12	0	—2	0
3	1	0	5	3·5	1·5	0	2	2	20	0	·5	0	·75	2·5	25	0	—·5	0
4	1·5*	0	8	0	2·5	0	1·5*	0	6	2	1·5	0	1*	0	1	7	—·5	0
5	2	0	12	0	1	0	3*	0	20	0	1·5	0	1*	0	4	2	—1	0
6	2*	0	9	0	1	0	·75·	0	9	6	1	0	·1·5	0	2	10	1·5	·3
7	1*	0	8	0	1	0	·5	0	8	1	1	0	—·5	0	1	3·5	·75	0
Av.	1·39	0·14	8·14	1·14	1·86	0·04	1·68	0·36	12·36	1·44	1·50	0·0	0·46	0·57	7·14	3·21	—·11	0·04

TABLE VI. CONGENITAL HEART DISEASE.

(THRILL AT PULMONARY CORTILAGE).

	LEAD I.						LEAD II.						LEAD III.					
	P	Q	R	S	T	U	P	Q	R	S	T	U	P	Q	R	S	T	U
1	1	0	10	0	1·5	·3	1	0	20	2	1·5	0	1	0	8	3	1	0
2	1·5	1	6	42	5	0	2	1	9	0	—2	0	—1	4	45	3	—7	0
3	2*	0	6	17	2·5	0	3*	1	7	4	2·5	0	·5*	5	20	0	·5	0
4	1	1	6·5	7	3	0	·5	1	18	12	2	0	—·5	3	17	7	—1	·3
5	1	0	4	20	4·5	·5	2	0	15	4	1	0	1·5	2	26	0	—4	0
6	2*	0	7	10	3	·5	3*	0	12	4	2·5	·3	1·5*	1	13	0	—·1	·3
7	2*	0	4	16	1	·5	6	2	11	0	1	·5	5	4·5	24	0	·5	·5
8	2	0	·5	14	1·5	0	2	1	5	5	2	·3	·5*	1·5	14	0	·5	0
9	1*	2	12	0	1·5	0	1*	0	21	9	3	0	2*	0	19	21	6	0
10							1*	0	6	3	2	0	1*	1	16	0	1·5	0
11	1	0	10·5	9·5	1	0	1	1·5	13	1·5	2	0	1	6·5	16	2	2	0
12	1	·5	4·0	17	2·5	0	3	1	8	3	-1·5	0	2	1·5	18	0	—4	0
Av.	1·41	0·41	6·41	13·86	2·45	0·16	2·12	0·71	12·08	3·96	1·33	0·09	1·21	2·50	19·67	3·0	—·42	0·09

*The summits or depressions so marked were double or notched.

Now changes in the electrocardiogram may be due not only to unilateral hypertrophy, but to displacement and, as is well known, the changes in displacement of the apex towards the left are not dissimilar to those supposed to represent an increase in the left muscle ; similarly for the right side.   It might be held therefore that the signs under consideration are in reality due, not to unilateral hypertrophy, but to alteration of the position of the heart as a consequence of hypertrophy.

This view is to my mind untenable, and for two reasons.   First, in frequent instances, the degree of change cannot be accounted for by displacement.   If R is represented by the values 5, 10 and 5 in the three leads respectively, the electric axis of the heart to a horizontal line drawn through the shoulders is according to Einthoven and his collaborators 60°.   Such values as are in the ratios of —5, 5, 10, respectively, in the same leads, would indicate an angle of 120°, and these values are not uncommonly expressed in cases of mitral stenosis.   Assuming the same original angle in the two series of patients, an average displacement of 60° to the right of the heart's axis must be postulated in the series with mitral stenosis.   Such displacement as a result of change of form is hardly conceivable.

Secondly, if the curve is altered by displacement the axis for the several deflections should be similarly altered.   If we compare normal curves with those obtained from cases of aortic disease, it is found that, upon the assumption of displacement, while the axis for R is generally moved to the left, the axis for T is generally moved to the right.   For R increases in Lead I, and diminishes in Lead III, while there is a decrease of T in Lead I and a relative increase in Lead III.

CLINICAL AND POST-MORTEM OBSERVATIONS.

In searching past writings for records of the relative condition of the two ventricles in different types of disease which are associated with hypertrophy, one is met by the primary difficulty that the majority of observers have been content to record their general experiences, or to report the condition of the right and left muscle as it appears to them upon opening the cavities of the heart.   Many of these observations have been of a cursory kind and the evidence produced is of a not very convincing order. It may be true that mitral stenosis is associated with preponderance of the right ventricle, and aortic disease and renal disease with preponderance of the left ; yet it is no easy task to find convincing proof of these conclusions in clinical writings of the past.   It seems to me essential that the question of hypertrophy and its associations with valvular disease should be placed once and for all upon a scientific basis and that a method of much greater exactitude than those customarily practised in the post-mortem room should be devised.   For experience has shown me that inspection of the heart in the fresh state, even when the organ is cut in several planes (Fig. 6), provides a very imperfect measure of the degree of hypertrophy of the muscle and of

its relative excess in one or other chamber. The evident fallacies which may creep in have been considered very fully by Müller, and I shall not pursue this subject further than to endorse his opinion that only such data are reliable as are gathered from careful dissection and weighing of the muscle.

Method of weighing. A method of weighing the muscle of the right and left heart has been described by Müller, but is I think less reliable than that which I adopt. Müller's hearts were cut in the fresh state and the lines of the cuts are described in insufficient detail. The technique of the present plan is as follows: The heart after removal of the parietal pericardium and great vessels is weighed and is fixed in 10% formalin for from four to seven days according to its size and in a distended condition ; it is then washed in running water for 24 to 48 hours and placed in 70% spirit. At the end of a week the pericardium and the whole of the subendocardial fat and coronary vessels are removed by careful dissection until the intact ventricular muscle is everywhere displayed ; the valves and chordæ tendineæ are removed and also all trace of adherent clot, be it of ante- or post-mortem origin.

The separation of the chambers of the ventricle is accomplished by a series of incisions (see Fig. 4). Large hearts are first bisected horizontally and the cuts in the upper portion of the ventricles are subsequently produced to the lower portion. The first incision is made parallel to the septum and at its junction with the right wall above and posteriorly ; as much of the right wall as is necessary is taken in to make the cut tangential to the septum where it joins the wall. This cut is continued downwards and should separate from the septum all loose ventricular trabiculæ and the papillary muscles. The second cut runs along the straight white fibrous line which unites the infundibulum to the septum and left ventricle (" conus tendon ") and is carried downwards so as to separate all loose ventricular trabiculæ, the representative of the moderator band and papillary muscles. On the anterior surface of the heart it lies in the inter-ventricular sulcus throughout its course, until it joins the posterior cut. If the cut has been made sufficiently generously it loosens the infundibulum as a complete muscular tube. The two cuts, prolonged to the apex of the ventricle should take away the whole of apical trabeculated portion, leaving no deep sulci upon the septal wall.

The third incision is made parallel to the first at the junction of left wall with septum above and posteriorly, and in such a line that it falls tangentially to the cavity of the left ventricle at the centre of the septum ; it passes into the second cut in front at approximately the centre of the white line and continuing downwards separates the left ventricle from the septum in such a fashion that the former remains an almost enclosed chamber from above downwards ; that is to say the vertical opening in the left ventricle which this septal cut makes is at the most 1 or 2 cm. in breadth.

The three portions of the ventricle are then laid in water and are weighed separately, the weighing being repeated at intervals of 24 hours until the weights are constant from day to day. Preliminary observations upon

intact hearts showed that the original weight of the muscle is restored with sufficient precision in this fashion.*

The method allows a full examination of each heart during the progress of the dissection. In cases where it is thought desirable to preserve the region of the auriculo-ventricular node and bundle for microscopic examination, this end may be attained by leaving the desired portion of the auricular septum in union with the ventricular, a separate portion of the auricular wall of the same approximate size being weighed and subsequently subtracted from the septum to obtain a truer septal weight. This procedure has been adopted in a few instances in the present series.

In the tables which follow, I give amongst other details the weight of the heart. This represents the whole heart weight with vessels cut short and parietal pericardium removed, and may be serviceable to those who are accustomed to express the mass of the heart in this fashion, inaccurate though it be. I give also the combined and separate weights of the two ventricles and septum and a further column in which the ratio of left and right is indicated. To obtain this index I neglect the septal weight and divide the weight of the left by that of the right ventricle.

Normal subjects : comparison with Müller's method.

Müller gives on page 214 of his thesis, a summary of his observations. He finds the average weight of the ventricular muscle in 154 unselected males of weights varying from 40-50 kilos, to be 194·8 grammes, for 137 females, 179·3 grammes.

For comparison with these figures, I give two control tables of selected cases (Table VII and VIII). The first is from 11 patients who died of carcinoma. They were for the most part males and the body weight averaged 49·4 kilos. The ventricular weight averaged 148·7 grammes, a figure considerably below that found by Müller. That the difference is not the result of accident is shown by my second table of controls, which includes 12 subjects dying of acute disease or accident and in which the average ventricular weight is 156·1 grammes. I attribute the lower ventricular weights of these tables to two causes, first the care with which the muscle fibres were laid bare and freed from fat, &c., and second to the nature of Müller's subjects, for a great number of them must unquestionably have had hypertrophy of the heart.

Müller also expresses the ratio of right and left ventricular weights ; for this purpose he divides the weight of the septum by calculation, apportions some to right and some to left ventricle, dividing the combined right weights by the combined left. For purposes of comparison I give, in additional columns in these two tables, the ratio as calculated by Müller's method. The average values for the tables are ·552 and ·565, respectively. Müller's

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* Naturally there is an increase of weight in the formalin stage ; a loss of weight in the alcohol stage and a final gain of weight when the heart lies in water.

TABLE VII. CANCER CONTROLS.

No.	Case No.	Age and Sex	Disease.	Body weight in kilos.	Heart weight in gms.	Vent. weight in gms.	R.	L.	S.	L./R.	Müller's ratio.	Remarks.
1	17	62 F	Carcinoma of caecum	42·1	283	104·0	36·0	54·0	14·0	1·50	·666	Heart and vessels normal. Exhaustion and collapse following excision.
2	43	43 F	Carcinoma of oesophagus	42·1	240	140·5	42·5	76·0	22·0	1·80	·539	Other organs normal. Tracheal obstruction the day following operation.
3	6	66 M	Carcinoma of tonsil	42·1	254	143·0	18·0	71·0	24·0	1·47	·676	Some slight arterial disease. Exhaustion.
4	9	66 M	Carcinoma of colon	43·3	368	182·5	50·5	102·0	30·0	2·02	·495	Coronaries tortuous. Calcareous deposits at base of aortic valves. Broncho-pneumonia 14 days after ileocolostomy.
5	57	55 F	Sarcoma of heart. General peritonitis	45·3	312	111·5	38·5	79·5	23·5	2·06	·484	Other organs normal. General peritonitis following operation.
6	65	56 F	Carcinoma of uterus	48·5		133·0	39·5	75·0	18·5	1·90	·526	A little atheroma of vessels. Collapse after operation.
7	48	M	Carcinoma of sigmoid colon	49·1	322	149·0	17·5	78·5	23·0	1·65	·665	Slight thickening of aortic valves but no incompetence. Perforation. General peritonitis.
8	31	45 M	Carcinoma of stomach	54·1	278	141·0	40·5	79·5	21·0	1·96	·509	Heart and arteries normal. Exhaustion.
9	28	32 M	Sarcoma of pelvis	57·1	290	177·5	49·0	101·0	27·5	2·06	·485	Cardiovascular system normal. General peritonitis.
10	37	50 M	Carcinoma of stomach	58·4	311	116·5	34·5	62·0	20·0	1·79	·557	See deposits in liver; other organs normal. Collapse following operation.
11	40	40 M	Sarcoma of mediastinum	61·2	379	207·5	60·0	117·0	30·5	1·45	·513	Cardiovascular system normal.
			Averages	49·4	304	148·7	44·2	81·4	23·1	1·83	·532	

TABLE VIII. CONTROLS.

No.	Case No.	Age and Sex	Disease	Body weight in kilos.	Heart weight in gms.	Vent.	R.	L.	S.	L/R	Müller's ratio.	Remarks.
1	108	29 F	Anorexia	24·0	198	111·5	31·5	64·0	16·0	2·03	·492	Cardiovascular system normal. Cystitis. Cervical endometritis. Mucous colitis.
2	30	20 F	Hydrochloric acid poisoning	28·6	200	104·5	31·5	60·0	13·0	1·90	·525	Cardiovascular system normal. Pyæmic abscesses.
3	14	33 M	Gastric ulcer	33·3	220	114·0	37·0	59·0	18·0	1·59	·627	Cardiovascular system normal. (General peritonitis.
4	18	36 M	Gastric ulcer	33·6	254	161·0	53·5	84·0	23·5	1·57	·637	Slight atheroma of aorta. Heart normal. Subphrenic abscess.
5	41	42 M	Actinomycosis of caecum	34·4	266	135·5	44·0	70·0	21·5	1·59	·629	Cardiovascular system normal. Bilateral psoas abscess.
6	2	14 M	Tumour of pineal body	35·7	206	111·0	28·0	60·0	23·0	2·14	·467	Cardiovascular system normal.
7	20	17 M	Fractured skull	40·3	339	169·0	53·0	86·0	30·0	1·62	·616	Cardiovascular system normal.
8	4	19 M	Tuberculous meningitis	48·6	297	202·0	49·0	107·0	46·0	2·18	·457	Cardiovascular system normal. Miliary tubercle of lungs.
9	7	34 M	Chronic encephalitis (Old fracture)	50·6	339	169·0	53·0	86·0	30·0	1·62	·616	Cardiovascular system normal.
10	8	30 M	Septic broncho-pneumonia	50·8	368	221·0	65·0	111·0	45·0	1·69	·586	Cardiovascular system normal.
11	56	64 M	Acute obstruction.	50·8	337	219·5	69·5	112·0	38·0	1·61	·613	Slight atheroma of aorta. Heart normal.
12	78	52 M	Acute pancreatitis	56·6	392	156·0	46·0	90·0	20·0	1·96	·511	Very slight atheroma of aorta. Heart normal.
			Averages	40·6	285	156·1	46·7	82·4	27·0	1·79	·565	

average figures for males and females of these weights are ·517 and ·522, respectively. The divergence in our results from this standpoint is not great therefore. Such divergence as exists is due to the methods of dividing the muscle. In the method which I describe, the cuts are more generous to the side walls of the ventricle, and this is very apparent upon comparison of his tables and my own, for my septal weights are low by comparison. The ratio R/L is greater in my tables than in Müller's and this is due I think to the inclusion of the whole of the trabecular network of the right ventricle in my right ventricular weights. The comparison between Müller's tables and my own shows that in respect of the relative weights of right and left ventricle, the average values for normal subjects is fairly constant, and that with small corrections, Müller's figures may be utilised if desired as a basis for abnormal hearts dissected in the manner I describe. Speaking with Müller's material and my own in view, the average ratio L/R for a small series of normal subjects will not vary beyond the limits 1·7 and 1·9. The average for a larger series will lie in the immediate neighbourhood of 1·8 ; that is to say, the left ventricle is 1·8 times as heavy as the right. The individual numbers of a series naturally vary to a considerable extent ; thus Table VII shows a variation from 1·47 to 2·06 ; and Table VIII a variation from 1·57 to 2·18. Such variations must be regarded as natural variations of normal subjects ; for Müller's tables show, even for newborn children and fœtuses of the last months of pregnancy, variations of 50% or more. The ratio L/R in its relation to valvular disease must be studied, therefore, in the average. The variation of L/R as a natural phenomenon is of interest in view of the electrocardiographic material collected by Gilder and myself.[7] We found in a number of apparently healthy students great variations in the types of curve obtained in the several leads, and divided the curves of our series into those which might be held to represent right and left-sided ventricular preponderance.

Pathological subjects.

The general plan of my observations has been to compare the physical signs during life with the weights of the muscle after death. The majority of the subjects included in the remaining tables were examined by me personally on a single occasion a few weeks or months before death, though a large number were examined on several occasions and notes of other observers were usually available. The physical signs to which special attention was paid were those stated to be serviceable in the differentiation of right or left hypertrophy, and those which might be of value in ultimately deciding the cause of the hypertrophy. The limits of heart dulness, the areas and nature of pulsations and shocks, the character of the heart sounds and murmurs, were signs universally noted. The action of the heart was recorded graphically when evidently abnormal. The systolic blood pressure was always taken in several readings with a Riva-Rocci apparatus. The arteries were examined for thickening of their walls.

At the post-mortem examination special attention was given to the condition of the lungs, pleuræ, pericardium, arteries and kidneys, sections being cut in almost every case from the last-named organs. The general results of these observations are tabulated with the heart weights, though I omit the detailed physical signs.

Observations upon the value of certain physical signs. After a close clinical examination of some 80 cases of hypertrophy of the heart and after comparing my notes with the weights of the separated chambers, I am compelled to conclude that such physical signs as are customarily utilised to differentiate left from right hypertrophy have little or no scientific value. While preponderance of one or other ventricle can be correctly surmised in some 70% or more of these patients before death,* it may be that such tests as are usually employed have a clinical value. As criteria in studying pathological processes they are quite unreliable.

I may exemplify these remarks by two illustrations. Amongst the physical signs vaunted as evidences of hypertrophy of the right ventricle, none perhaps commands greater respect at the present time than pulsation in the epigastrium. I have examined this sign somewhat minutely, attending to two separate phenomena, each of which when present is quite unmistakeable. I refer to pulsation visible to the observer as he watches the epigastrium in a patient who lies in bed, and to the thrust of the heart, which may be felt by the hand, pressed backwards and it may be a little upwards or to the left from the same region. My results as they were obtained in 53 subjects are given in the accompanying table (Table IX). This table is divided to show the relation which right ventricles of different weights have to the signs in question ; such evidence as it presents is, if anything, in a direction contrary to that anticipated.

TABLE IX.

Epigastric signs of right hypertrophy (53 cases).

Weight of right ventricle.	Under 80 grammes. Epigastric		80-100 Epigastric		100-150 Epigastric		Over 150 Epigastric	
	Pulse	Thrust	Pulse	Thrust	Pulse	Thrust	Pulse	Thrust
Absent	8 (42%)	11 (58%)	3 (20%)	5 (36%)	6 (37·5%)	10 (59%)	0	3
Present	5 (26%)	4 (21%)	4 (21%)	5 (36%)	4 (37·5%)	2 (12%)	1	
Conspicuous	6 (32%)	4 (21%)	8 (53%)	4 (28%)	6 (24%)	5 (29%)	1	
Total	19	19	15	14	16	17	2	3

Of a forcible and thrusting maximal impulse, displaced perhaps downwards and to the left, as a clinical test of left hypertrophy, one may speak more favourably. It has been found for the most part in patients who have

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* I question if it is correctly surmised in this percentage without the help which knowledge of the valve lesions brings.

subsequently shown enlarged left ventricles, though not exclusively. As a sign of left preponderance it has far less value. A most notable instance of the unreliability of these physical signs utilised as tests in pathological studies, may be cited in *CASE* 74, Table X. The post-mortem revealed a remarkable condition ; a left ventricle of 132 grammes (normal 120·7, Müller), not materially enlarged for a man of 69 kilos., appearing as an appendage of an enormous right chamber of 411 grammes (normal 66·1, Müller). The most prominent pulsation before death was a heaving impulse in the 6th left space, 5½ inches from the mid-line and due, as events showed, to the right ventricle, which formed the apex of the heart (see Fig. 2 and 3) ; of epigastric pulse or thrust nothing could be detected.

These facts are of importance because in judging of the relation of new physical signs to hypertrophy of one or other chamber, it is permissable to be guided only by signs which have been *proved by investigation of chamber weights* to be invariable or almost invariable evidences of the conditions to which they may be thought to bear witness.

Mitral stenosis. Weights of the ventricles have been taken from 33 cases of mitral stenosis in all. The details of these cases are to be found in Tables X, XI and XII. The average weight of the ventricles is 270·3 grammes (normal for females 208·3, and for males 232·9 grammes, Müller, for bodies of 50-60 kilos.). The average relation of L R is 1·73, a figure which does not vary greatly from normal. The average figures of this series show hypertrophy of the whole heart, which is relatively more conspicuous in the right chamber. Of the 33 cases, 17 had aortic disease also, the aortic lesions being slight in 6 instances and considerable in 11. The remaining 16 cases (mitral stenosis) show an average L/R ratio of 1·55. But even this figure is too high a value to associate with the valve lesion pure and simple ; it is raised by the inclusion of *CASES* 9, 11, 12, 13, 14, 15 and 16. These patients had either renal lesions or high blood pressure. An examination of Table X shows quite clearly that mitral stenosis is responsible for considerable preponderance of the right ventricle and that on the whole the degree of preponderance runs hand in hand with the degree of mitral constriction. In all instances of mitral stenosis the diastolic size of the mitral orifice was measured post-mortem and the cases of Table X are arranged according to the degree of constriction. It is in the young subject with greatly constricted orifice that the greatest preponderance of the right ventricle is seen. In six cases of mitral stenosis dissected and weighed by Hirsch[2] by Müller's method, the average value of L/R was 1·00 ; the ventricles had on an average equal weights.

If we take a series of cases of mitral stenosis, especially if such a series is uncomplicated by aortic valve lesions, or high blood pressure, we may be certain that we shall deal with a series in which there is an average relative preponderance of the right ventricle. Average electrocardiographic curves of cases of this kind show Einthoven's sign of this preponderance (Fig. 1).

TABLE X. MITRAL STENOSIS.

No.	Case No.	Age and Sex.	Body weight in kilos.	Heart weight in gms.	Vent.	R.	L.	s.	$\frac{L}{R}$	Mitral stenosis.	Other valve defects.	Kidneys.	Syst. B.P.	Remarks.
1	95	61 F		297	162·0	54·5	78·0	29·5	1·43	48 s.m. Button-hole	A little tricuspid stenosis	A little fibrosis, &c. Old infarcts	175	Arteries thickened. Pericard. universally adherent. Coronaries fair. Lung and pleuræ nil. Cardiac failure. (A.F.)*
2	29	33 F		482	248·0	137·0	68·0	43·0	0·50	50 s.m. Funnel	Mitral regurgitation	Practically normal. Congested	138	A few fine pericardial adhesions. Arteries, coronaries lung and pleuræ normal. Extrasystoles. Cardiac failure.
3	33	39 F			147·5	69·0	57·0	21·5	0·83	109 s.m. Button-hole	Nil	Practically normal. Congested		Arteries and coronaries v. fair. Pericardium, lungs, pleuræ nil. Cardiac failure.
4	63	36 M	64·0	553	287·0	128·0	105·0	54·0	0·82	115 s.m. Button-hole.	Nil	Practically normal. Congested	110-120	Arteries and coronaries v. fair. Pericardium, lungs nil. One pleura adherent. Cardiac failure. (A.F.)
5	25	53 F		436	192·0	96·5	64·5	31·0	0·67	180 s.m. Funnel	Mitral regurgitation	Practically normal. Congested	110-140	Arteries and coronaries v. fair. Pericardium, lungs, pleuræ nil. Cardiac failure. (A.F.)
6	55	42 F	49·9	397	215·0	67·5	114·0	33·5	1·69	220 s.m.	Tricuspid 413 s.m. Stenosed	Practically normal. Congested	108-120	Arteries and coronaries v. fair. Pericardium, lungs, pleuræ nil. Cardiac failure.
7	15	42 F	55·2	524	219·5	77·5	109·5	32·5	1·41	230 s.m. Funnel	Tricuspid 309 s.m. Stenosed. Mitral regurgitation	Practically normal. Congested		Arteries and coronaries v. fair. Pericardium, lungs, pleuræ nil. Cardiac failure. (A.F.)
8	36	56 F	29·0	218	108·0	38·5	51·0	18·5	1·32	250 s.m. Funnel	Nil	Normal. Congested		Arteries and coronaries atheromatous. Pericardium, lungs, pleuræ nil. Appendix abscess; Operation.
9	80	80 F		256	132·0	38·5	70·5	23·0	1·83	345 s.m.	Mitral regurgitation	Granular kidneys	160	Arteries atheromatous. Coronaries thickened. Right lung universally, left partially, adherent; old tubercle. Perforated colicul·er. Extrasystoles

10	74	36 M	69·0	1048	632·0	411·0	132·0	89·0	0·32	347 s.m.	Mitral regurgitation. Widely patent foramen ovale. Pulm. ring dilated but apparently competent	Practically normal.	115	Aorta, arteries healthy. Coronary a little sclerosed; lungs, pleura, pericardium nil. Cardiac failure.
11	89	45 F	58·5	708	418·5	88·0	251·0	79·5	2·85	445 s.m.	Nil	Granular	180-230	Arterial sclerosis. Coronaries atheromatous, the left plugged; pericardium, pleuræ, lungs nil. Cardiac failure.
12	79	54 F		468	232·0	69·5	128·0	34·5	1·84	450 s.m.	Nil	Slight fibrosis. Congested	200-215	Vessels atheromatous, coronaries patchy atheroma; pericardium, pleuræ, lungs nil. Cardiac failure.
13	97	56 M		553	371·5	75·0	231·5	65·0	3·09	450 s.m.	Mitral regurgitation	Granular	250-270	Vessels and coronaries atheromatous. Old tubercle in lungs. Pleuræ, pericardium nil. Cardiac failure.
14	84	62 F	49·9	425	234·0	75·0	120·0	39·0	1·60	455 s.m.	Mitral regurgitataon	Granular	220-260	Arteries and coronaries atheromatous; pericardium, lungs, pleuræ nil. Cardiac failure. (A.F.)
15	24	42 F		408	213·5	48·0	124·0	41·5	2·58	500 s.m.	Mitral regurgitation	Granular		Arteries and coronaries almost normal. Recent pericarditis. Lungs and pleuræ normal. Cardiac failure.
16	71	66 M	60·8	546	294·0	82·5	168·5	43·0	2·02	550 s.m.	Mitral regurgitation	Syphilitic endarteritis and fibrosis	160-170	Arteries very atheromatous, slightly. Coronary orifices narrowed. Both pleuræ universally adherent. Lungs and pericardium nil. Cardiac failure.
Averages ..	..	..	55·7	488	256·7	97·3	117·0	42·4	1·55					

*A.F. = auricular fibrillation.

TABLE XI. MITRAL STENOSIS (WITH SLIGHT AORTIC LESIONS).

No.	Case No.	Age and Sex	Body weight in kilos.	Heart weight in gms.	Vent.	R.	L.	S.	$\frac{L}{R}$	Mitral stenosis.	Aortic valves.	Other valve defects.	Kidneys.	Syst. B.P.	Remarks.
1	100	58 F	44·5	368	156·5	46·0	88·5	22·0	1·92	48 s.m. Button-hole.	Regurg. 4 s.m. No stenosis.	Mitral regurg.	Scattered fibrosis, &c.	—	V. sl. atheroma of arteries. Coronaries v. fair. Emphysematous lungs. Pericard., pleuræ nil. Cardiac failure.
2	83	83 M		439	189·0	110·0	57·5	21·5	0·52	49·5 s.m.	Regurg. A few sq. m. No stenosis	Nil	A little fibrosis, &c.	130-135	Sl. atheroma arteries and coronaries. Left pleura adherent. Pericard., lungs nil. Cardiac failure. (A.F.)
3	47	76 F		514	240·5	55·5	142·5	42·5	2·56	450 s.m.	Regurg. A few s.m. No stenosis	Nil	Granular	180-190	Arteries and coronaries atheromatous, coronary orifices narrowed. A few pericardial adhesions. Pleuræ, lungs nil. Cardiac failure. (A.F.)
4	61	M		708	372·0	100·0	222·0	50·0	2·22	460 s.m.	Regurg. A few sq. m. No stenosis	Mitral regurg.	Normal but for infarcts and congestion	—	Arteries and coronaries atheromatous. Pericard., lungs, nil. Rt. pleura adherent. Cardiac failure. (A.F.)
5	67	66 M		483	266·0	60·5	164·0	41·5	2·71	550 s.m.	V. sl. stenosis No Incompetence	Mitral regurg.	Large congested	194	Arteries and coronaries atheromatous. Emphysema. Pleuræ and pericard. universally adherent. Carcinoma of pancreas.
6	53	73 F		439	233·0	43·0	147·5	42·5	3·43	600 s.m.	V. sl. stenosis. A few s.m. Regurg.	Mitral regurg.	Granular	245-250	Arteries and coronaries v. atheromatous. Pleuræ adherent. Pericard. and lungs nil. Uræmia. (A.F.)
Averages..	..	..		492	242·8	69·2	137·0	36·6	2·23						

But we are not to expect the sign in all cases of the series, for the ratio L/R is very variable for different members of the series ; instances of mitral stenosis in which there is a relative preponderance of the left ventricle are by no means uncommon ; and no factor appears to be more potent in reversing the preponderance than raised arterial tension (see Table X). In six cases of mitral stenosis, with systolic blood pressure of 180 mm. Hg. and over, the ratio L/R was on the average 2·75.

Aortic disease. My tables include 30 cases in which aortic lesions were present. Seventeen of these were cases (Table XI and XII) complicated by mitral stenosis in greater or less degree. For the whole series of aortic cases, the average ventricular weight was 343·2 grammes ; the ratio L R was 2·00. In 13 cases of aortic disease, uncomplicated by mitral stenosis (Table XIII) the ventricular weights averaged 421·7 grammes and L/R was 2·15. But as in mitral stenosis individual values of L R are very variable and even in uncomplicated aortic disease L R often falls within normal limits or may indicate a relative excess of the right muscle. These facts and the lesser divergence of L R from the normal in aortic cases, as opposed to mitral stenosis, harmonize with electrocardiographic observations upon similar series of patients. Because a patient has aortic mischief, Einthoven's sign of left preponderance cannot be anticipated ; it may be predicted only in the average curve of a series of such cases.

While 2·00 is the ratio of L R for all my aortic cases, four of these patients who exhibited high blood pressure gave an average of 2·62 for L/R. The average value in eight aortic cases recorded by Hirsch was 2·62.

ELECTROCARDIOGRAPHIC CURVES AND POST-MORTEM OBSERVATIONS.

The observations which I have so far recorded were undertaken because the electrocardiographic curves often seemed incompatible with other physical signs as they are understood to-day. Investigation has thrown doubt upon the value of these signs ; and has clearly shown the wide variation from right to left preponderance which may occur in individual cases of a given form of valvular disease. In brief, the electro-cardiographic signs in various forms of valvular affections are by no means incompatible with our knowledge of hypertrophy in these conditions. On the other hand there appears to be harmony.

Evidently the question may be put to more direct tests : a comparison of curves and weights from the same cases is eminently desirable. Such a comparison is to be seen in the ten cases of Table XIX. The cases have been tabulated from above downwards in the order determined by the measurements of the electrocardiograms. The first cases presented curves

TABLE XII. MITRAL STENOSIS AND AORTIC DISEASE.

No.	Case No.	Age and Sex	Body weight in kilos.	Heart weight in gms.	Vent.	R.	L.	S.	L/R	Mitral stenosis.	Aortic valves.	Other valve defects.	Kidneys.	Syst. B.P.	Remarks.
1	109	42 F	65·3	558	285·0	101·0	139·5	44·5	1·38	37 s.m.	Regurg. 17 s.m. No stenosis	Mitral regurg. Tricuspid stenosis. 406 s.m.	Considerable diffuse fibrosis		Arteries and coronaries healthy. Lungs, pericard. pleura nil. Cardiac failure.
2	85	85 M		397	152·0	53·5	60·5	38·0	1·13	60 s.m.	Regurg. and stenosis. 31·5 s.m. Fused segments	Tricuspid stenosis. 290 s.m.	Scattered fibrosis, &c.	100	Arteries and coronaries almost normal. Lungs, pleura and pericard. nil. Cardiac failure. (A.F.)
3	103	25 F	43·5	433	270·5	84·0	146·0	40·5	1·74	80 s.m. Funnel	Regurg. and stenosis. 77 s.m. Fused segments	Mitral regurgitation	Normal Congested		Arteries and coronaries nil. Lungs, pleura and pericardium nil. Cardiac failure. (A.F.)
4	99	18 M		416	246·0	88·5	113·5	44·0	1·28	128 s.m. Funnel	Regurg. 11 s.m. stenosis. 98 s.m.	Mitral regurg.	Normal Engorged	125- 130	Arteries and coronaries nil. Rt. pleura universally adherent. Lungs, pericard. nil. Cardiac failure. (A.F.)
5	88	16 F	45·1	595	331·5	108·0	179·5	44·0	1·66	132 s.m.	Regurg. 24·5 s.m. No stenosis	Mitral regurg. Tricuspid 702 s.m.	Normal Congested	100- 106	Arteries and coronaries normal. Lungs, pericard. pleura nil. Cardiac failure.

No.	Case	Age/Sex										Mitral regurg.	Normal except for few infarcts, etc.		Arteries, etc.
6	60	54 F	51.7	460	292.0	98.5	158.0	35.5	1.60	220 s.m.	Regurg. 16.5 s.m. No stenosis	Mitral regurg.	Normal except for few infarcts	130-136	Arteries and coronaries very fair. Lungs, pericardium, pleura nil. Cardiac failure. (A.F.)
7	101	37 M	87.9	744	423.5	112.0	243.0	68.5	2.17	260 s.m. Funnel	Regurg. a few s.m. Stenosis 94 s.m.	Nil	Chronic parenchymatous nephritis	160	Slight atheroma, aorta and coronaries. Lungs, pleurae, pericard. nil. Uraemia.
8	69	65 F	48.4	496	324.5	75.5	193.5	55.5	2.56	333.5 s.m.	Calcified Regurg. and stenosis 55 s.m.	Nil	Granular	160-220	Very atheromatous arteries and coronaries. Lungs, pleurae, pericard. nil. Cardiac failure.
9	87	30 F		539	364.5	108.0	199.0	57.5	1.84	384 s.m.	Regurg. and stenosis 130 s.m.	Mitral regurg.	Chronic parenchymatous nephritis	145	Aorta atheromatous. Coronaries nil. Lungs, pleura, pericardium nil. Pneumonia.
10	105	36 M		610	370.0	119.0	195.0	56.0	1.64	465 s.m.	Regurg. 6 s.m. Extensive stenosis calcareous.	Mitral regurg.	Advanced arteriosclerotic	120	Syphilitic aortitis. Coronaries healthy. Lungs, pleurae nil. Recent pericarditis. Cardiac failure.
11	59	57 F	70.0	471	297.0	86.5	157.5	63.0	1.82	575 s.m.	Regurg. 13.2 s.m. No stenosis	Mitral regurg. Tricuspid 986 s.m.	Slight fibrosis. Old infarcts	148-165	Arteries patchy atheroma. Coronary orifices narrowed. Lungs, pleurae, pericard. nil. Cardiac failure.
Averages	..	..	58.7	520	305.1	94.0	162.3	48.8	1.71						

TABLE XIII. AORTIC DISEASE.

No.	Case No.	Age and Sex.	Body weight in kilos	Heart weight in gms.	Vent.	R.	L.	s.	L/R	Aortic valves.	Other valve defects.	Coronary arteries.	Kidneys.	Syst. B.P.	Remarks.
1	16	69 M		580	343·0	103·5	177·5	62·0	1·71	Regurg. and stenosis 40 s.m.	Mitral regurg.	Orifices narrowed, vessels v. atheromatous	Sl. interstitial and arterial changes	155	General arterial atheroma. Pericard., pleura, lungs nil. Cardiac failure.
2	81	26 M		785	549·5	140·0	318·0	91·5	2·27	Stenosis considerable. Free regurg.	,,	Normal	Normal but for congestion and single infarct.	135	Rheumatic. Arteries very fair. Pericardium, pleura, lungs nil. Cardiac failure.
3	52	50 M	57·1	719	386·0	103·0	224·0	59·0	2·17	Stenosis. Free regurg.	Nil.	A little atheromatous	Scattered fibrosis, &c. Old infarcts.	145	Syphilitic. Arterial sclerosis. Emphysema. Pericard. universally adherent (fresh). Pleura nil. Cardiac failure.
4	102	62 M	88·9	666	330·5	100·0	184·0	46·5	1·84	Stenosis considerable. No regurg.	Mitral regurg.	Almost normal	V. slight fibrosis. Old infarct.	−185	Arteries atheromatous. Pericardium universally adherent. Lungs, pleura, nil. Cardiac failure. (A.F.)
5	66	61·M		650	358·0	107·5	196·0	54·5	1·82	No stenosis. Regurg. 230 s.m.	,,	—	Large. Little change	170	Arteries atheromatous. Lungs emphysematous. Pericard. and pleura nil. Cardiac failure.
6	23	41 M	62·1	878	559·5	106·5	366·5	86·5	3·44	No stenosis. Regurg. 188 s.m.	,,	Orifices greatly narrowed. Vessels atheromatous.	Congested only	160	Syphilitic. Aorta sclerosed, dilated. Pericardium, lungs, pleura nil. Cardiac failure.

No.	Age & Sex									Mitral	Orifices	Fibrosis		Remarks
7	2	56 M	65·8	650	343·0	91·5	187·0	64·5	2·04	A little stenosis. Regurg. 92 s.m.	Mitral regurg.	Orifices greatly narrowed. Vessels sclerosed	Scattered fibrosis	150·	Syphlitic. Advanced sclerosis of aorta. Pericardium, lungs, pleurae nil. Cardiac failure.
8	44	47 M	68·5	1005	667·0	145·0	382·5	139·5	2·74	No stenosis. Regurg. 58 s.m.	Mitral regurg.	Rt. orifice occluded. Left v. small. Vessels atheromatous	Large. Syphlitic endarteritis.	140-190	Syphlitic. Advanced sclerosis of aorta. Pericard., lungs, pleurae nil. Cardiac failure.
9	26	66 M		629	377·0	140·0	178·0	59·0	1·27	Sl. stenosis. Regurg. 30 s.m.	Mitral regurg.	Vessels calcareous.	Large. Some interstitial change	100	Arteries atheromatous. Emphysema, old tubercle. Pericardium, pleurae nil. Cardiac failure.
10	73	38 M	63·5	619	409·0	117·5	219·0	72·5	1·86	Sl. stenosis. Regurg. 12 s.m.	Mitral regurg.	Rt. orifice obliterated Left small. Vessels sclerosed	Normal congested	120-170	Syphlitic. Aorta very sclerosed. Pericardium, lungs, pleurae nil. Cardiac failure. Extrasystoles.
11	46	85 F		551	180·5	47·0	106·0	27·5	2·26	No stenosis Regurg. 10 s.m.	Mitral regurg.	Vessels sclerotic	Granular	·140	Rheumatic. Advanced atheroma of arteries. Pleura and pericardium universally adherent. Lungs nil. Cardiac failure. (A.F.)
12	104	44 M	59·7	877	563·0	135·0	362·0	66·0	2·68	No stenosis Regurg. 7 s.m.	Nil	Vessels calcareous	Little change	130·	Rheumatic and syphilitic. Aorta sclerosed. Pericardium pleura, lungs nil. Cardiac failure.
13	107	42 M	62·3	656	416·5	129·0	241·0	46·5	1·87	Sl. stenosis. Regurg. 3 s.m.	Nil	Orifices narrowed. Vessels healthy	Large, some vascular change		
Averages ..		66·0	713	421·7	112·7	241·7	67·3	2·15						

TABLE XIV. INSTERTITIAL NEPHRITIS (CONTRACTED KIDNEYS), &c.

No.	Case No.	Age and sex.	Body weight in Kilos.	Heart weight in gms.	Vent.	R.	L.	S.	L./R.	Valve defects.	Kidneys.	Syst. B.P.	Remarks.
1	27	60 M		680	386·5	98·5	217·5	70·5	2·20	Mitral regurg.	102 grm. Typical red granular contracted*	187-195	Lead poisoning. General arterio-sclerosis. Coronaries normal. Lungs, pleura, pericardium nil. Cardiac failure.
2	11	59 F		512	268·0	86·0	136·0	46·0	1·58	Nil. Aortic cusps thickened but competent	168 grm. Typical red granular contracted	125	13 years duration. Patchy atheroma of vessels. Coronaries normal. Emphysema. A few pericardial adhesions. Pleura nil. Cardiac failure.
3	13	69 M		480	201·0	83·5	90·5	27·0	1·08	Mitral regurg.	170 grm. Typical red granular, contracted.	190	Syphlitic. Aortic sclerosis; coronaries slight thickening. Lungs, pleura, pericardium nil. Cirrhosis of liver. Cardiac failure. (A.F.)
4	94	66 F		510	276·5	70·0	162·0	44·5	2·31	Nil. Aortic cusps thickened but competent.	184 grm. Contracted.† Arterio-sclerotic.	160	Arteries atheromatous. Rt. coronary orifice narrow, vessels atheromatous, calcareous. Pleura, lungs, pericardium nil. Cardiac failure.
5	34	76 M		480	238·0	96·5	107·5	34·0	1·11	Mitral regurg. Aortic cusps a little calcified but competent.	190 grm. Typical red, granular, contracted.	160	Arteries patchy atheroma. Right coronary orifice narrow. Vessels atheromatous. Lungs, pleura, pericardium nil. Uræmia.

6	96	56 M	44·0	567	341·0	106·0	186·0	49·0	1·75	Very slight aortic leak (2 s.m.).	198 grm. Contracted. Arterio-sclerotic.	175	Little arterial disease. Coronaries, a few atheromatous patches. Lungs, pleuræ, pericardium nil. Uræmia and cardiac failure.
7	45	79 M	63·5	442	232·5	62·0	138·0	32·5	2·22	Nil.	203 grm. Typical red, granular contracted.	110-120	Arteries atheromatous. Rt. coronary orifice narrowed; vessels atheromatous. Lungs, pleuræ nil. Pericard. a few adhesions. Cardiac failure. (A.F.)
8	38	63 M	—	511	280·0	76·0	155·5	48·5	2·05	Mitral regurg.	213 grm. Contracted. Arterio-sclerotic.	190-208	Gout. Arteries sclerosed. Coronaries sclerosed. Lungs, pleuræ, pericard. nil. Cardiac failure. (P.A., V. Ex.)††
9	82	42 M	88·9	411	284·0	68·5	167·0	48·5	2·41	Nil.	240 grm. Typical red, granular, contracted.	220	Arterial disease slight. Slight atheroma of coronaries. Some emphysema. Pleuræ, pericardium nil. Cardiac failure.
10	10	76 M	70·7	570	345·0	95·0	185·0	65·0	1·95	Mitral regurg.	247 grm. Typical red, granular, contracted.	140	General arterial atheroma. Coronaries atheromatous. Lungs, pleuræ, pericard. nil. Cardiac failure.
Averages ..	..	..	67·0	516	285·5	84·2	154·5	46·5	1·87				

* Small, red, granular surface, adherent capsule, cortex reduced, dense interstitial fibrosis and lymphocytosis, hyaline Malpighian corpuscles numerous; vascular thickening.

† Changes the same, profound but more patchy, deep scarring, vascular changes prominent.

†† P.A. = Pulsus alternans. V. Ex. = Ventricular extrasystoles.

TABLE XV. INTERSTITIAL NEPHRITIS (LESS ADVANCED), &c.

No.	Case No.	Age and Sex	Body weight in kilos	Heart weight in gms.	Vent.	R.	L.	S.	R/L	Valve defects	Kidneys	Syst. B.P.	Remarks
1	54	70 M	64·5	638	351·5	92·0	214·5	45·0	2·33	Nil.	255 grm. Early red granular, contracted.	205	Arteries and coronaries atheromatous. Emphysema and old tubercular scarring in lungs. Pleuræ, pericard. nil. Cardiac failure.
2	54a	67 M		652	305·0	81·0	187·5	36·5	2·32	Mitral regurg.	260 grm. Typical, red, granular, early.	150-160	Arteries atheromatous; coronaries slightly so. Healed tubercle at lung apices. Pleuræ, pericard. nil. Uræmia, cardiac failure. (A.F.)
3	75	63 M	57·1	626	375·0	88·5	213·0	73·5	2·41	Calc. deposits at bases of aortic valves competent. 247·5 s.m. Perphps sl. sten.	269 grm. Diffuse fibrosis. Vessels thickened.	225-220	Arteries and coronaries sclerosed. Lungs, pleuræ, pericardium nil. Cardiac failure and uræmia.
4	77	66 F	45·8	495	298·5	79·5	169·5	49·5	2·13	Mitral regurg.	299 grm. Early arterio-sclerotic.	150	Arteries and coronaries atheromatous. Left pleura universally adherent. Lungs, pericard. nil. Cardiac failure. (P.A. Ex.)
5	35	64 M	60·2	695	356·0	104·0	191·0	61·0	1·84	Nil.	312 grm. Diffuse fibrosis. Internal thickening of vessels.	190-200	Syphilitic. Sl. atheroma of arteries, more of coronaries. Emphysema. Pericardium, pleura nil. Cardiac failure and uræmia.

6	72	68 M		585	421·5	108·0	251·0	62·5	2·32	Nil.	57 grm. fibrosis. Dense 280 grm. Diffuse fibrosis. Vascular.	150	Arteries and coronaries atheromatous. Lungs, pleura, pericard. nil. Cardiac failure. (Ex.)
7	86	60 M		681	402·5	113·5	235·5	53·5	2·07	Nil.	380 grm. Diffuse fibrosis. Intimal thickening of vessels.	190·	Arteries and coronaries atheromatous. Emphysema Pleura, pericardium nil. Uræmia.
8	58	55 M		524	308·5	90·5	175·5	42·5	1·94	Nil.	397 grm. Diffuse fibrosis. Vessels thick.	150·185	Arteries and coronaries atheromatous. Lungs, pleura, pericard. nil. Uræmia, cardiac failure.
Averages	53·0	37·2	612	352·3	94·6	204·7	53·0	2·17					

TABLE XVI.

RENAL INVOLVEMENT OF LESS DEFINED TYPE.

(Similar to the last group but with lesser grades of renal involvement.)

No	Case No.	Age and Sex.	Body weight in kilos.	Heart weight in gms.	Vent.	R.	L.	S.	$\frac{L.}{R.}$	Valve defects.	Kidneys.	Syst. B.P.	Remarks.
1	32	45 F	82·6	390	152·0	36·5	90·0	25·5	2·47	Mitral regurg.	269 grm. A few hyaline glomeruli, sparse interstitial changes.	144	Arteries and coronaries very fair. Emphysema. Pericardium and pleuræ nil. Cardiac failure.
2	19	63 M		467	241·0	64·0	135·0	42·0	2·11	Mitral regurg.	524 grm. A few hyaline glomeruli. Distended ragged tubules. Arterial changes.		Arteries and coronaries very fair. Cirrhotic liver. Lungs, pleuræ, pericardium nil. Cardiac failure. (A.F.)
3	68	64 M		542	289·5	76·5	165·0	48·0	2·16	Mitral regurg.	311 grm. Some fibrosis, a few cysts and hyaline glomeruli.	·170	General arterial disease; coronaries v. atheromatous. Emphysema. Pericard., pleuræ nil. Cardiac failure. (A.F.) and uræmia.
4	98	56 M		549	330·5	139·0	149·0	42·5	1·07	Nil.	345 grm. A few hyaline glomeruli. Sl. fibrosis. Engorged.		General arterial disease; one coronary a little constricted, otherwise fair. Emphysema, left pleuræ adherent. Lungs nil. Cardiac failure. (A.F.)

	No.	Age & Sex											
5	1	45 F	80·5	550	324·5	112·5	171·5	40·5	1·52	Nil.	438 grm. A good deal of fibrosis and lymphocytosis. Vascular.	130. 150	Aorta slightly atheromatous, coronaries healthy. Lungs, pleuræ, pericard. nil. Cardiac failure.
6	51	59 M	61·7	562	306·0	85·0	177·0	44·0	2·08	Nil.	394 grm. Slight interstitial changes, scarring. Vascular.	160	Arteries and coronaries v. fair. Lungs, pleuræ, pericard. nil. Cardiac failure (A.F.) and gangrene of legs (thrombotic).
7	90	58 M		575	404·0	120·5	216·5	67·0	1·80	Mitral regurg.	406 grm. Slight fibrosis and lymphocytosis. A few cysts. Congested.	·140	Arterial disease. Atheroma of coronaries. Rt. pleura adherent. Lungs and pericard. nil. Cardiac failure. (A.F.)
8	42	69 M	77·4	610	373·5	100·0	213·0	60·5	2·13	Nil.	390 grm. Slight fibrosis, few hyaline glomeruli Lymphocytosis. Vascular.	·160	General arterial disease; coronaries fair. Slight emphysema. Pleuræ, pericard. nil. Cardiac failure. (A.F.)
9	93	63 M	68·2	697	408·5	118·0	220·0	70·5	1·86	Mitral regurg.	421 grm. Slight fibrosis and lymphocytosis. Scarring. Vascular.	·160	Syphilitic. General arterial disease. Coronary orifices narrow. Vessels calcareous. Right branch thrombosed. Pleuræ adherent. Pericard. nil. Cardiac failure. (A.F.)
Averages			74·1	550	314·4	94·7	170·8	48·9	1·91				

TABLE XVII. UNCLASSIFIED.

No.	Case No.	Age and Sex.	Body weight in kilos	Heart weight in gms.	Vent.	R.	L.	S.	L/R	Valve defects.	Kidneys.	Syst. B.P.	Remarks.
1	2	45 M	689	626	368·5	113·5	203·0	52·0	1·79	Nil	Normal, congested	140	Rheumatic. Arteries and coronaries normal. Lungs, pleura, pericardium nil. Cardiac failure. (A.F.)
2	76	54 F		722	319·0	140·0	131·0	48·0	0·94	Nil	Normal, congested	120	Some atheroma. Coronaries normal. Lungs, pleura, pericardium nil. Cardiac failure.
3	91	42 M	751	1100	608·0	147·0	345·0	116·0	2·35	Mitral regurg		150-180	Syphilitic. Arteries v. fair. Coronaries practically normal. Lungs, pleura, pericardium nil. Cardiac failure. (Ex. P.A. Bundle branch lesion.)

TABLE XVIII. RESPIRATORY DISEASE.

No.	Case No.	Age and Sex	Disease.	Body weight in kilos.	Heart weight in gms.	Vent.	R.	L.	S.	L/R	Remarks
1	39	37 M	Advanced tuberculosis of lungs and testicles.	32·7	363	169·0	52·5	94·0	22·5	1·79	Cardiovascular system normal.
2	70	40 M	Pulmonary tuberculosis. Very extensive fibrocaseous disease with cavitation (19 months history). Both pleurae universally adherent.	44·5		159·0	53·5	82·0	23·0	1·53	Cardiovascular system normal.
3	49	52 M	Advanced emphysema and bronchitis of many years duration.	61·0		182·5	68·5	84·0	30·0	1·23	Cardiovascular system normal.
4			Advanced emphysema and bronchitis of many years duration.			275·0	101·0	111·0	63·0	1·09	

TABLE XIX.

ELECTROCARDIOGRAMS AND MUSCLE WEIGHTS COMPARED.

Case No	Lead I.					Lead II.					Lead III.					Heart weight.	Vent. weight.	R.	L.	S.	L./R.	Disease.
	P	Q	R	S	T	P	Q	R	S	T	P	Q	R	S	T							
110	1	1	8	1	-1·5	2	·5	4	10	4	1	0	3	15	5	583	270·5	68	174	28·5	2·6	Angina pectoris.
2	1·5	·5	12·5	1	1	2	0	9	1	1	1	0	1	8·5	0	650	343	91·5	187	64·5	2·04	Aortic disease.
107	1	0	10	1	2	2	0	5	8	5	2	0	3·5	7	4	656	416·5	129	241	46·5	1·87	Aortic disease.
58	1	0	8	0	0	2·5	0	11	2·5	1	2	0	3	3	1	524	308·5	90·5	175·5	42·5	1·94	Renal disease.
59	1	0	6	1	1·5	1·5	0	5	2·5	1	1	0	2	1·5	0	471	297	86·5	157·5	53·0	1·82	Mitral stenosis and Aortic disease.
109	1	0	1	1	·5	2	0	5	6·5	3	1	0	4	5·5	2·5	558	285	101	139·5	44·5	1·38	Mitral stenosis and aortic disease.
60	-	0	1	4	1	-	0	6	3	2	1	0	5	1	1	400	292	98·5	158	35·5	1·60	Mitral stenosis and aortic disease. (A.F.)
63	-	0	·5	8	2	-	0	8	5	-1/+1	·	0	11	3	-2/+1	553	287	128	105	54	0·82	Mitral stenosis and auricular fibrillation.
—	2	1	6	41	4	2	1	9	1	-3	+1/-1	3	44	2	-6	—	256	161	67	28	0·41	Congenital pulmonary stenosis.

showing Einthoven's sign of left preponderance, the last case the curves of
right preponderance.*   For comparison with these curves I give the muscle
weights and the ratio L/R in a separate column.

With two minor exceptions the order of the ratio L/R is the anticipated
order.   Considering the variations to which the position of the hypertrophied
heart is subject and the natural variations in the arrangement of its fibres
from organ to organ, the correspondence between the electrocardiographic
signs and the muscle weights is remarkably close.

GENERAL REMARKS UPON HYPERTROHPY.

As has been said, my object in undertaking the work which is here
recorded, was to investigate the value of certain electrocardiographic signs
of hypertrophy, and to compare such signs with those now in general use
as bedside tests. The results in so far as they affect these questions have been
discussed and we have seen that the observations lend distinct support
Einthoven's views ; we have seen too that they give prominence to
Einthoven's signs as tests of the pathological changes when the value of
these signs is weighed against that of other clinical tests. Many of the
latter are unquestionably worthless for exact work. My remarks should
perhaps end at this point ; yet, with the present collection of material I
cannot refrain from offering some general observations upon hypertrophy.

In the foreground I would place a fact which has become increasingly
apparent as these studies have progressed. It is that in studying hypertrophy,
the usual method, simple inspection of the organ, is quite insufficient and that
a method of weighing the muscles of the separate chambers is alone reliable.
In expressing this opinion I am but reiterating the views of Müller who
first adopted this method, and of others, such as Krehl,[5] who have devoted
much attention to the subject. Yet the method of weighing has not been
adopted, as I think it should have been, in pathological departments of
teaching institutes, neither is it employed by those who infer a large personal
experience of hypertrophy in its relation to valve or renal defects. Repeated
opportunities of comparing the actual weight of the ventricles with recorded
opinions of the separate muscle masses, gauged by inspection, leads me to
attach but little value to such opinions. Since our present day conceptions†
of clinical hypertrophy are based almost exclusively upon observations of
this kind, the need of extensive and accurate measurements and of an
unbiassed revision of these conceptions, becomes very evident.

The view that hypertrophy is secondary to increased work, and that
such hypertrophy is manifested by those heart chambers upon which the
increased burden falls, is paramount to-day. That increased work is
followed by hypertrophy of the heart muscle which experiences it I do not

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* The arrangement is controlled by the following arbitrary formula $(R^1$ minus $R^3)$ +
$(S^3$ minus $S^1)$ where R and S represent the heights of the peaks in the leads indicated.

† A broad and very accurate account of hypertrophy general has been written by Krehl[5].

deny ; that such is the case has been clearly shown by experiments which admit no serious fallacy[2,8,9]. The theory finds full support in clinical observations upon mitral stenosis, such as these now presented. But that change in the mechanical conditions of the circulation are the sole or even

TABLE XX.

THE AVERAGES OF TABLES VII-XVIII.

Disease.	No. of Cases.	Body weight	Heart weight.	Vent.	R.	L.	S.	L/R.
Mitral stenosis	16	53·7	488	256·7	97·3	117·0	42·4	1·55
Mitral stenosis and slight aortic disease	6	—	492	242·8	69·2	137·0	36·6	2·23
Mitral stenosis and aortic disease	11	58·7	520	305·1	94·0	162·3	48·8	1·89
All mitral stenosis cases	33	56·4	500	270·3	91·1	135·7	43·5	1·73
Six of these cases with B.P. of 180 or over	6	53·4	524	307·6	68·6	185·9	53·1	2·75
Aortic disease alone	13	66·0	713	421·7	112·7	241·7	67·3	2·15
All aortic cases	30	61·5	598	343·2	97·2	191·6	54·4	2·00
Four aortic cases with B.P. of 180 or over	4	78·6	521	288·5	69·7	172·2	46·5	2·62
Interstitial nephritis (advanced)	10	67·0	516	285·2	84·2	154·5	46·5	1·87
Four of these cases with B.P. of 180 or over	4	?88·9	520	287·6	81·6	157·6	48·6	1·94
Interstitial nephritis (less advanced)	8	53·0	612	352·3	94·6	204·7	53·0	2·17
Four of these cases with B.P. of 180 or over	4	58·6	660	271·2	99·5	213·5	58·2	2·16
Renal cases of less defined type	9	74·1	550	314·4	94·7	170·8	48·9	1·91
All renal cases	27	64·5	556	314·8	90·8	174·8	49·3	1·97
All patients (15) with B.P. of 180 or over	15	67·0	569	320·8	82·4	185·6	52·8	2·31
Cancer controls	11	49·4	304	148·7	44·2	81·4	23·1	1·83
Controls	12	40·6	285	156·1	46·7	82·4	27·0	1·79

the chief causes of hypertrophy has not been proved. The hypertrophy which follows experimental lesions of the aortic valves is a hypertrophy chiefly of the left ventricle. as Stewart[9] has shown, but it is equally clear from his observations that the degree of hypertrophy which results from lesions of this kind is in no way comparable to the hypertrophy found in many clinical instances of the same defect. The average increase found by Stewart in the weight, is an increase of 40% ; the greatest increase is less

than 100%. In the human subject the average increase is 60%,* and, what is of greater significance, it may amount to 280% or more. That is to say, while the aortic lesion may be held fully to account for the hypertrophy of the smaller hearts so damaged, the mechanical factor is insufficient to explain those examples which come within the ill-defined category of *cor bovinum*. While it is impossible, after a close survey of data, such as those presented by Tables X to XIII to deny that the mechanical cause is often a most potent one, and that the degree of valve defect and degree of hypertrophy are often parallel, yet it is impossible to overlook the frequent and considerable discrepancies in this relation. Thus in mitral stenosis combined with aortic disease, the left ventricle is relatively more preponderant (see values L/R in Table XX) where the aortic lesion is slight than where it is severe. " Idiopathic hypertrophy " still developes secretly ; but the term, or what it implies, namely, hypertrophy of unknown cause, is restricted too rigidly to hearts in which *no* cause is apparent. It is not applied to instances of *insufficient* cause. Some of the largest hearts discovered (see No. 3, Table XVII) belong to the " idiopathic " group. Some cause beyond our ken is responsible for the great enlargement ; may not the same unknown cause be the chief cause in many greatly enlarged hearts in which the valve lesions are comparatively insignificant (see No. 8, Table XIII, and No. 10, Table X)? My plea is that these questions should be re-opened, and studied upon a more exact basis, and that hypertrophy when discovered should not be attributed to this or that mechanical factor, until the influence and degree of influence of such factor is fully appreciated.

Another feature of my tables which deserves attention is the relative frequence of general hypertrophy of the heart. Hypertrophy of the left ventricle alone is seen in aortic disease only very exceptionally, 1 case in 13 (No. 11, Table XIII) ; in 5 cases of the same series the relation of left to right is within normal limits, while in a single instance, the right ventricle is predominant. Thus out of 13 cases, left preponderance is shown by 7 only. In simple mitral stenosis the left ventricle is small on the other hand and exceptionally (No. 5, Table X) may be reduced in weight, as Hirsch has also found. It is in renal disease especially that general and uniform hypertrophy is frequently discovered (compare Hirsch's statements[3]). Thus the average muscle weight in ten cases of advanced interstitial nephritis (Table XIV) was 285 grammes ; the ratio between left and right ventricles averaged 1·87, a normal figure. In aortic disease it is the rule that the heaviest heart shows the greatest left preponderance, but in renal the reverse is as often the case. The factor which immediately influences the size of the heart in renal disease still remains obscure. In my own series, the ventricles were heavier in interstitial nephritis of less advanced type (Table XV) than in the cases of really shrunken kidney (in the former 352 grammes, in the latter

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* Muller's figure for the average weight of the male ventricles, body weight 60-70 kilo, is 266 grammes ; in 13 cases of aortic disease of average body weight 60 kilo, it was 422 grammes.

285 grammes). In the third renal group tabulated (Table XVI), which includes those of chiefly vascular origin the ventricles are heavy (average 314 grammes), but here again the ratio of left and right is normal (1·91). In the complete series of 27 renal cases the ratio is 1·97 ; a normal value. Hirsch's conclusions and my own are in accord : apparently it is not true that in patients dying of renal disease the left ventricle is preponderant ; the hypertrophy is uniform.

In producing preponderance of the left ventricle no factor seems more potent than raised blood pressure, and this fact accords with present conceptions. though so far as I am aware no exact observations have ever been made in this direction. Thus in 15 subjects who were found to have blood pressures of 180 or more before death, the ratio of left ventricle and right was 2·31. But if these cases are sub-divided some curious facts are noticed. The group in which the highest ratio is found (namely 2·75) is the group of high pressure cases associated with mitral stenosis ; next to these in order come the pressure cases and aortic disease (ratio 2·62) and finally the renal cases (ratio 2·16 and 1·94).

This brief discussion may suffice to re-awaken interest in a subject which to my mind requires a far more detailed and prolonged study than it has so far received. I am content to note the chief features exhibited by my own tables, calling attention especially to observations which appear to be at variance with current teaching in this country. Evidently, before we can consider our knowledge of hypertrophy in relation to valvular or renal disease to be at all complete, the number of hypertrophied hearts studied must be multiplied.

SUMMARY AND CONCLUSIONS.

1. A method of dissecting and weighing the human ventricles is described, which may be adopted as a basis for more exact measurement of hypertrophy than has hitherto been undertaken.

2. An examination of the physical signs, checked by post-mortem observations leads me to the conclusion that those signs which are customarily employed at the bedside are of little real value in differentiating between right and left ventricular preponderance.

3. Einthoven's signs of right or left preponderance have much evidence in their favour. The signs of right preponderance in aortic disease, or of left preponderance in mitral stenosis, occasionally observed, are apparent rather than real discrepancies, for it can be shown that corresponding predominance of the muscle on one or other side may exist in association with the valve lesions in question.

4. It is probable that mechanical factors are by no means the only important causes of hypertrophy of the heart.

5. The commonest type of hypertrophy is a uniform hypertrophy. In renal disease this is the rule. In aortic disease it is almost as frequent as is hypertrophy with preponderance of the left ventricle.

6. High blood pressure appears to be especially potent in creating a preponderance of the left ventricle.

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Fig. 5.

Fig. 6.